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ORIGINAL PAPER

Reactivity of substrates with multiple competitive reactive sites toward NBS under neat reaction conditions promoted by visible light

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Abstract

Regioselectivity of visible-light-induced transformations of a range of (hetero)aryl alkyl-substituted ketones bearing several competitive reactive sites (α-carbonyl, benzyl and aromatic ring) with *N*-bromosuccinimide (NBS) was studied under solvent-free reaction conditions (SFRC) and in the absence of inert-gas atmosphere, radical initiators and catalysts. An 8-W energy-saving household lamp was used for irradiation. Heterogeneous reaction conditions were dealt with throughout the study. All substrates were mono- or dibrominated at the α-carbonyl position, and additionally, some benzylic or aromatic bromination was observed in substrates with benzylic carbon atoms or electron-donating methoxy groups, respectively. Surprisingly, *ipso*-substitution of the acyl group with a bromine atom took place with (4-methoxynaphthyl) alkyl ketones. While the addition of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxy) decreased the extent of α- and ring bromination, it completely suppressed the benzylic bromination and α,α-dibromination with NBS under SFRC.

Keywords Halogenation · Photochemistry · Solvent-free reaction conditions · NBS · Regioselectivity

Introduction

Solvent-free reaction conditions (SFRC) (Tanaka and Toda 2000; Metzger 1998) are alternative reaction conditions to the transformations in solution (Reichardt 2007) and attracted considerable attention due to important advantages. Shorter reaction times, lower consumption of organic solvents, simple isolation/purification procedures and less reaction waste are some of notable advantages. Nonconventional reaction media, such as water, supercritical CO_2 or ionic liquids, are also a promising replacement for organic solvents (Adams et al. 2004). Another alternative is to perform reactions under highly concentrated reaction conditions (Walsh et al. 2007) or in the presence of a small amount of solvent vapor (Nakamatsu et al. 2005). A great number of different reactions under (SFRC) have been reviewed in both older and more recent literature (Cave et al. 2001; Martins et al. 2009; Singh and Chowdhury 2012; Gawande et al. 2014; Obst and König 2018; Zagande and Patil 2019).

N-bromosuccinimide (NBS) is one of the most common and versatile reagents in organic chemistry (Djerassi 1948; Paquette et al. 2009). It is easy to handle, inexpensive, readily available, non-toxic, and usually more selective than bromine. Traditional methods of bromination include molecular bromine or bromides under harsh reaction conditions, even though unconventional methods, for instance, in water (Shaw et al. 1997; Tanaka et al. 1999) or under SFRC (Toda and Schmeyers 2003; Pravst et al. 2009; Wang and Gao 2012), have been developed. In a more alternative approach, transformations with NBS are performed under microwave and ultrasound irradiation (Heropoulos et al. 2007), on water (Podgoršek et al. 2006), in ionic liquids (Togo and Hirai 2003; Ganguly et al. 2005), $scCO_2$ (Tanko and Blackert 1994) and bio-waste extract (Appa et al. 2019). Under SFRC, aromatic (Prakash et al. 2004; Imanzadeh et al. 2006), Wohl–Ziegler (Winkler et al. 2014) and α-bromination of carbonyl compounds (Kumar et al. 2012; Pravst et al. 2008) have been reported, but these methods still require the use of acid catalysts or radical initiators. While more activated substrates react in the absence of catalysts

In memory of Dr. Miha Tišler (1926–2021), Professor Emeritus of University of Ljubljana.

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or initiators (Rahman et al. 2005; Pravst et al. 2006a, b, 8; Bose and Mal 2014), other methods make the use of alternative modes of activation, such as microwave irradiation (Goswami et al. 2004) or concentrated solar radiation (Dinda et al. 2013; Deshpande et al. 2015). Photo-induced transformations with NBS have been extensively studied in solvents (Arbuj et al. 2007; Šterk et al. 2013; Cantillo et al. 2014); however, to the best of our knowledge there are rare reports on these reactions under SFRC (Jereb et al. 2009).

Molecular motion in solvent-free reactions is restricted, and the aggregate state of the reaction mixture plays an important role in SFRC transformations. Whereas molecules are more mobile in liquid/solid systems, between two solid reagents, the formation of a melt phase is crucial for increased molecular mobility (Rothenberg et al. 2001). More so than the aggregate state, the structure of the substrates largely affects the reactivity and selectivity of transformations. We have previously shown that a 40-W tungsten lamp promotes benzylic-, ring- or α-carbonyl bromination by NBS under SFRC (Jereb et al. 2009). One might wonder how selective bromination under visible-light conditions would be when a competitive aromatic-, radical- and α-carbonyl substitution was possible in a single substrate. Studies addressing this issue have been reported (Pravst et al. 2006a, b, 47; Podgoršek et al. 2009; Vražič et al. 2013), but in those cases regioselectivity of functionalization was modulated through careful tuning of the reaction conditions. To our knowledge, regioselectivity of visible-light-induced transformations of substrates containing several competitive reactive sites with NBS under SFRC remains unexplored.

In the present study, we investigated photochemical transformations of diverse aryl-substituted ketones with NBS under solvent-free reaction conditions: with an 8-W energy-saving lamp as an activation source, in the absence of any solvents, radical initiators and catalysts and in the presence of air. For testing the substrate scope, we selected a broad range of liquid and solid ketones that contained different functional groups, which could have an influence on the type of transformation.

Experimental

General information

Reagents and solvents were obtained from commercial sources. NBS was recrystallized from a mixture of CH_2Cl_2/petroleum ether, and solvents were used as received. All ketones were prepared by the method of the classical Friedel–Crafts acylation (Vogel et al. 1989). **14** was prepared according to the published procedure (Coan and Becker 1955).

Reactions were performed in closed flasks without inert atmosphere. The experimental procedure was the same for liquid and solid ketones: NBS was added to the substrate and the reaction mixture was stirred with a small stirring bar under solvent-free reaction conditions (SFRC). Reaction mixtures with solid ketones turned into a molten state and the reaction proceeded as efficiently as the reactions with liquid substrates. An 8-W energy-saving lamp was used throughout all the experiments, and the average reaction temperature was 27 °C. The experiments in the dark were carried out at 27 °C. The progress of the reactions was monitored by thin-layer chromatography (TLC). Light source: Philips Genie 8 W energy-saving light bulb. Column chromatography (CC): silica gel 60 (63–200 mm, 70–230 mesh ASTM; Fluka); CH_2Cl_2/petroleum ether (1:3). Preparative thin-layer chromatography (TLC): Merck-60-F_{254} plates; mixtures of light petroleum ether (b.p. 40–60 °C) and CH_2Cl_2. NMR spectra: Bruker DPX 300 (300 MHz) and Bruker AVANCE III (500 MHz) instruments; in $CDCl_3$; δ in ppm relative to TMS as internal standard for ^{1}H NMR and to the central line of $CDCl_3$ (δ = 77.00 ppm) for ^{13}C NMR, J in Hz. IR spectra: Bruker Alpha FT-IR spectrometer; in cm^{-1}. HRMS: Agilent 6224 Accurate Mass TOF LC/MS system spectrometer; electrospray ionization; in m/z. Elemental analysis: Perkin Elmer CHNS/O Analyzer 2400 Series II elemental analyzer. Melting points: Büchi 535 melting point apparatus; uncorrected.

General procedure for photo-induced reactions with NBS under SFRC

To a ketone (0.3 mmol), NBS (0.33 or 0.66 mmol, 20 or 39 mg) was added and the resulted reaction mixture was stirred under illumination with an 8-W energy-saving light bulb for 19–29 h. At the end of the reaction, conversions and the product distribution were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Pure products were obtained after separation by either CC or preparative TLC and were analyzed by ^{1}H NMR, ^{13}C NMR, IR, HRMS and melting point when solid. Spectroscopic data of the known compounds are available in Supporting Information and are in accordance with the literature data.

Characterization of the new products

2-Bromo-1-(4-(isopropyl)phenyl)ethanone 2c.

1c (0.049 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel (R_f = 0.55, CH_2Cl_2/petroleum ether 1:3 → 2:1). Colorless oil (0.028 g, 39%). IR (neat): ν 2961, 1676, 1604, 1569, 1461, 1416, 1310, 1278, 1198, 1186, 1056, 1009, 990, 846, 822, 677, 661 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (*d*, *J* = 6.9 Hz, 6H), 2.98 (sept,

$J = 6.9$ Hz, 1H), 4.44 (*s*, 2H), 7.35 (*d*, $J = 8.3$ Hz, 2H), 7.93 (*d*, $J = 8.3$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.6, 30.9, 34.3, 127.0, 129.2, 131.8, 155.7, 190.9. HRMS (ESI-TOF, *m/z*): found 241.0223 ($[M+H]^+$, $C_{11}H_{14}BrO^+$; calc. 241.0223).

2-Bromo-1-(3-methyl-4-methoxyphenyl)ethanone **2e.**

1e (0.049 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.47$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Colorless solid (0.013 g, 18%). M.p. 45–48 °C. IR (neat): ν 2941, 1683, 1596, 1497, 1438, 1410, 1250, 1212, 1126, 1020, 878, 818, 752, 682, 611 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (*s*, 3H), 3.91 (*s*, 3H), 4.40 (*s*, 2H), 6.87 (*d*, $J = 8.6$ Hz, 1H), 7.80 (*d*, $J = 1.7$ Hz, 1H), 7.86 (dd, $J = 1.7$, 8.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3, 30.8, 55.6, 109.4, 126.4, 127.3, 129.3, 131.5, 162.4, 190.2. HRMS (ESI-TOF, *m/z*): found 243.0013 ($[M+H]^+$, $C_{10}H_{12}BrO_2^+$; calc. 243.0015).

2-Bromo-1-(3,5-dimethyl-4-methoxyphenyl)ethanone **2f.**

1f (0.053 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.38$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Pale yellowish solid (0.015 g, 19%). M.p. 43–45 °C. IR (neat): ν 2948, 1682, 1595, 1483, 1387, 1313, 1256, 1229, 1140, 1055, 1007, 887, 856, 769, 708, 641 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 6H), 3.77 (s, 3H), 4.41 (s, 2H), 7.67 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3, 30.9, 59.7, 129.5, 130.0, 131.6, 162.0, 190.7. HRMS (ESI-TOF, *m/z*): found 257.0172 ($[M+H]^+$, $C_{11}H_{14}BrO_2^+$; calc. 257.0172).

2-Bromo-1-(4-(1-bromoethyl)phenyl)ethanone **3b.**

1b (0.044 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Preparative TLC ($R_f = 0.45$, CH_2Cl_2/petroleum ether 1:3). Brownish solid (0.002 g, 4%). M.p. 48–53 °C. IR (neat): ν 2948, 1694, 1603, 1571, 1412, 1388, 1280, 1197, 1162, 1069, 1042, 989, 822, 681 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (*d*, $J = 6.9$ Hz, 3H), 4.42 (*s*, 2H), 5.20 (*q*, $J = 6.9$ Hz, 1H), 7.52–7.59 (*m*, 2H), 7.94–8.00 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 30.6, 47.5, 127.4, 129.4, 133.7, 149.1, 190.6. HRMS (ESI-TOF, *m/z*): found 304.9168 ($[M+H]^+$, $C_{10}H_{11}Br_2O^+$; calc. 304.9171).

2,2-Dibromo-1-(4-(isopropyl)phenyl)ethanone **4c.**

1c (0.049 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.68$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Yellowish solid (0.011 g, 21%). M.p. 40–45 °C. IR (neat): ν 2961, 1684, 1599, 1567, 1460, 1414, 1311, 1270, 1223, 1198, 1055, 983, 850, 840, 770, 742, 709, 682 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (*d*, $J = 6.9$ Hz, 6H), 2.99 (sept, $J = 6.9$ Hz, 1H), 6.69 (*s*, 1H), 7.36 (*d*, $J = 8.4$ Hz, 2H), 8.02 (*d*, $J = 8.4$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5, 34.4, 39.8, 127.1, 128.5, 130.0, 156.3, 185.6. HRMS (ESI-TOF, *m/z*): found 318.9330 ($[M+H]^+$, $C_{11}H_{14}Br_2O^+$; calc. 318.9328).

2,2-Dibromo-1-(4-(cyclohexyl)phenyl)ethanone **4d.**

1d (0.061 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.75$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Colorless solid (0.003 g, 5%). M.p. 100–104 °C. IR (neat): ν 3027, 2920, 2848, 1683, 1600, 1566, 1445, 1416, 1315, 1273, 1212, 1191, 1145, 988, 841, 774, 707, 630 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21–1.32 (*m*, 1H), 1.35–1.49 (*m*, 4H), 1.74–1.81 (*m*, 1H), 1.82–1.93 (*m*, 4H), 2.54–2.63 (*m*, 1H), 6.70 (*s*, 1H), 7.34 (*d*, $J = 8.3$ Hz, 2H), 8.01 (*d*, $J = 8.3$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.9, 26.6, 33.9, 39.9, 44.8, 127.5, 128.4, 129.9, 155.5, 185.6. HRMS (ESI-TOF, *m/z*): found 358.9634 ($[M+H]^+$, $C_{14}H_{17}Br_2O^+$; calc. 358.9641).

2,2-Dibromo-1-(3-methyl-4-methoxyphenyl)ethanone **4e.**

1e (0.049 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.68$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Colorless solid (0.015 g, 29%). M.p. 113–115 °C. IR (neat): ν 3033, 2923, 1665, 1591, 1503, 1455, 1438, 1416, 1259, 1217, 1127, 1022, 987, 908, 814, 761, 717, 680, 615 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (*s*, 3H), 3.92 (*s*, 3H), 6.70 (*s*, 1H), 6.88 (*d*, $J = 8.7$ Hz, 1H), 7.88 (*d*, $J = 2.1$ Hz, 1H), 7.97 (dd, $J = 2.1$, 8.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3, 40.0, 55.7, 109.5, 122.8, 127.6, 130.1, 132.2, 162.9, 184.9. HRMS (ESI-TOF, *m/z*): found 320.9117 ($[M+H]^+$, $C_{10}H_{11}Br_2O_2^+$; calc. 320.9120).

2,2-Dibromo-1-(3,5-dimethyl-4-methoxyphenyl)ethanone **4f.**

1f (0.053 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.48$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Colorless solid (0.014 g, 25%). M.p. 85–87 °C. IR (neat): ν 2940, 1688, 1593, 1479, 1310, 1221, 1142, 994, 903, 776, 749, 715, 652 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (*s*, 6H), 3.79 (*s*, 3H), 6.71 (*s*, 1H), 7.75 (*s*, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3, 39.8, 59.8, 126.2, 130.7, 131.8, 162.5, 185.4. HRMS (ESI-TOF,

m/z): found 334.9276 ($[M+H]^+$, $C_{11}H_{13}Br_2O_2^+$; calc. 334.9277).

2-Bromo-1-(4-(methylthio)phenyl)propan-1-one **6c.**

5c (0.054 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel (R_f = 0.60, CH_2Cl_2/hexane 1:3 → 2:1). Pale brownish solid (0.053 g, 68%). M.p. 88–90 °C. IR (neat): ν 2988, 1666, 1583, 1405, 1346, 1247, 1192, 1164, 1093, 1058, 992, 944, 830, 768, 745, 689 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.89 (*d*, *J* = 6.6 Hz, 3H), 2.53 (*s*, 3H), 5.25 (*q*, *J* = 6.6 Hz, 1H), 7.28 (*d*, *J* = 8.5 Hz, 2H), 7.93 (*d*, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.7, 20.1, 41.4, 125.0, 129.3, 130.1, 146.9, 192.3. HRMS (ESI-TOF, *m/z*): found 258.9785 ($[M+H]^+$, $C_{10}H_{12}BrOS^+$; calc. 258.9787).

2-Bromo-1-(5-methyl-2-methoxyphenyl)propan-1-one **6d.**

5d (0.053 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel (R_f = 0.59, CH_2Cl_2/hexane 1:2 → 2:1). Yellowish oil (0.056 g, 73%). IR (neat): ν 2925, 1671, 1608, 1495, 1463, 1441, 1404, 1332, 1283, 1248, 1178, 1160, 1136, 1020, 968, 809, 741, 607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (*d*, *J* = 6.7 Hz, 3H), 2.31 (*s*, 3H), 3.89 (*s*, 3H), 5.53 (*q*, *J* = 6.7 Hz, 1H), 6.86 (*d*, *J* = 8.5 Hz, 1H), 7.23–7.31 (*m*, 1H), 7.49–7.54 (*m*, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 20.3, 48.0, 55.8, 111.5, 125.4, 130.4, 131.7, 134.5, 156.1, 196.6. HRMS (ESI-TOF, *m/z*): found 257.0164 ($[M+H]^+$, $C_{11}H_{14}BrO_2^+$; calc. 257.0172).

2-Bromo-1-(3-bromo-4,5-dimethoxyphenyl)propan-1-one **6e.**

5e (0.058 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel (R_f = 0.42, CH_2Cl_2/petroleum ether 1:3 → 2:1). Yellowish oil (0.024 g, 42%). IR (neat): ν 2934, 1695, 1592, 1505, 1439, 1372, 1336, 1257, 1204, 1158, 1045, 1024, 972, 897, 855, 790, 760, 630 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.91 (*d*, *J* = 6.7 Hz, 3H), 3.90 (*s*, 3H), 3.92 (*s*, 3H), 5.40 (*q*, *J* = 6.7 Hz, 1H), 7.03 (*s*, 1H), 7.06 (*s*, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.9, 45.6, 56.2, 56.3, 110.6, 113.2, 115.9, 130.8, 148.4, 151.7, 196.6. HRMS (ESI-TOF, *m/z*): found 350.9225 ($[M+H]^+$, $C_{11}H_{13}Br_2O_3^+$; calc. 350.9226).

2-Bromo-1-(4-(bromomethyl)phenyl)propan-1-one **7a.**

5a (0.044 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Preparative TLC (R_f = 0.51, CH_2Cl_2/petroleum ether 1:3). Colorless solid (0.010 g, 20%). M.p. 80–83 °C. IR (neat): ν 2928, 1675, 1604, 1438, 1417, 1345, 1235, 1205, 1155, 1093, 993, 948, 857, 823, 767, 723, 702, 635 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.90 (*d*, *J* = 6.6 Hz, 3H), 4.50 (*s*, 2H), 5.26 (*q*, *J* = 6.6 Hz, 1H), 7.51 (*d*, *J* = 8.2 Hz, 2H), 8.00 (*d*, *J* = 8.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0, 31.9, 41.4, 129.4, 129.4, 133.8, 143.4, 192.6. HRMS (ESI-TOF, *m/z*): found 304.9171 ($[M+H]^+$, $C_{10}H_{11}Br_2O^+$; calc. 304.9171).

2-Bromo-2-methyl-1-(4-methylphenyl)propan-1-one **9a.**

8a (0.049 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Preparative TLC (R_f = 0.64, CH_2Cl_2/petroleum ether 1:3). Pale yellowish oil (0.017 g, 23%). IR (neat): ν 2927, 1672, 1606, 1459, 1370, 1267, 1163, 1104, 978, 886, 827, 748, 677 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.03 (*s*, 6H), 2.41 (*s*, 3H), 7.24 (*d*, *J* = 8.2 Hz, 2H), 8.07 (*d*, *J* = 8.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 31.7, 60.5, 128.8, 130.4, 131.9, 143.2, 196.3. HRMS (ESI-TOF, *m/z*): found 241.0221 ($[M+H]^+$, $C_{11}H_{14}BrO^+$; calc. 241.0223).

2-Bromo-1-(2,4-dimethylphenyl)-2-methylpropan-1-one **9b.**

8b (0.053 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel (R_f = 0.63, CH_2Cl_2/petroleum ether 1:3 → 2:1). Pale yellowish oil (0.041 g, 53%). IR (neat): ν 2972, 2924, 1688, 1612, 1458, 1385, 1369, 1257, 1126, 1102, 973, 875, 817 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.97 (*s*, 6H), 2.26 (*s*, 3H), 2.34 (*s*, 3H), 6.98–7.03 (*m*, 1H), 7.06 (*s*, 1H), 7.60 (*d*, *J* = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.1, 21.3, 30.7, 62.6, 125.5, 126.9, 131.8, 134.9, 135.9, 139.8, 202.2. HRMS (ESI-TOF, *m/z*): found 255.0379 ($[M+H]^+$, $C_{12}H_{16}BrO^+$; calc. 255.0379).

2-Bromo-1-(3-methyl-4-methoxyphenyl)-2-methylpropan-1-one **9d.**

8d (0.058 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Preparative TLC (R_f = 0.40, CH_2Cl_2/petroleum ether 1:5). Yellowish oil (0.013 g, 16%). IR (neat): ν 2928, 1664, 1598, 1501, 1458, 1386, 1317, 1298, 1256, 1127, 1104, 1021, 986, 916, 817, 760, 681, 617 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.04 (*s*, 6H), 2.25 (*s*, 3H), 3.90 (*s*, 3H), 6.83 (*d*, *J* = 8.7 Hz, 1H), 7.99 (*d*, *J* = 2.0 Hz, 1H), 8.15 (dd, *J* = 2.0, 8.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3, 32.0, 55.5, 60.6, 108.7, 126.4, 126.4, 130.6, 133.1, 161.3, 195.2. HRMS (ESI-TOF, *m/z*): found 271.0329 ($[M+H]^+$, $C_{12}H_{16}BrO_2^+$; calc. 271.0328).

2-Bromo-1-(4-(bromomethyl)phenyl)-2-methylpropan-1-one **10a.**

8a (0.049 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Preparative TLC (R_f = 0.48, CH_2Cl_2/petroleum ether 1:3). Yellowish solid (0.012 g, 23%). M.p. 36–38 °C. IR (neat): ν

2979, 1668, 1603, 1451, 1411, 1388, 1264, 1230, 1203, 1163, 1102, 979, 887, 849, 820, 764, 713, 679, 606 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.03 (*s*, 6H), 4.50 (*s*, 2H), 7.46 (*d*, $J = 8.4$ Hz, 2H), 8.13 (*d*, $J = 8.4$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.5, 32.1, 60.2, 128.8, 130.7, 134.6, 142.0, 196.1. HRMS (ESI-TOF, *m/z*): found 318.9329 ($[M+H]^+$, $C_{11}H_{13}Br_2O^+$; calc. 318.9328).

2-Bromo-1-(3-(bromomethyl)-4-methoxyphenyl)-2-methylpropan-1-one **10d.**

8d (0.058 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Preparative TLC ($R_f = 0.21$, CH_2Cl_2/petroleum ether 1:5). Colorless solid (0.011 g, 18%). M.p. 79–81 °C. IR (neat): ν 2929, 1655, 1595, 1503, 1458, 1444, 1265, 1223, 1142, 1105, 1034, 1018, 1001, 937, 916, 842, 819, 763, 617 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.04 (*s*, 6H), 3.97 (*s*, 3H), 4.57 (*s*, 2H), 6.91 (*d*, $J = 8.8$ Hz, 1H), 8.22 (*d*, $J = 2.3$ Hz, 1H), 8.26 (dd, $J = 2.3$, 8.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.1, 31.8, 55.9, 60.4, 110.0, 125.9, 126.8, 133.4, 133.6, 160.7, 194.5. HRMS (ESI-TOF, *m/z*): found 348.9432 ($[M+H]^+$, $C_{12}H_{15}Br_2O_2^+$; calc. 348.9433).

2-Bromo-1-(4-methoxyphenyl)-2-phenylethan-1-one **12b.**

11b (0.068 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.47$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Pale yellowish solid (0.055 g, 60%). M.p. 67–70 °C. IR (neat): ν 2928, 1671, 1601, 1571, 1508, 1452, 1422, 1357, 1312, 1264, 1217, 1173, 1027, 846, 824, 774, 734, 688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.85 (*s*, 3H), 6.36 (*s*, 1H), 6.89–6.93 (*m*, 2H), 7.29–7.38 (*m*, 3H), 7.51–7.55 (*m*, 2H), 7.95–8.00 (*m*, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 51.1, 55.5, 114.0, 126.9, 128.9, 129.0, 129.0, 131.5, 136.3, 163.9, 189.6. HRMS (ESI-TOF, *m/z*): found 305.0165 ($[M+H]^+$, $C_{15}H_{14}BrO_2^+$; calc. 305.0172).

2-Bromo-1-(5-methyl-2-methoxyphenyl)-2-phenylethan-1-one **12c.**

11c (0.120 g, 0.5 mmol), NBS (0.107 g, 0.6 mmol). Column chromatography on silica gel ($R_f = 0.45$, CH_2Cl_2/hexane 1:2 → 2:1). Yellowish solid (0.100 g, 63%). M.p. 44–46 °C. IR (neat): ν 2943, 1676, 1607, 1579, 1495, 1453, 1401, 1285, 1246, 1157, 1126, 1020, 810, 695, 626 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (*s*, 3H), 3.85 (*s*, 3H), 6.59 (*s*, 1H), 6.81 (*d*, $J = 8.5$ Hz, 1H), 7.21–7.36 (*m*, 4H), 7.44–7.53 (*m*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 55.1, 55.7, 111.5, 125.5, 128.6, 128.6, 129.4, 130.5, 131.9, 134.8, 136.5, 155.9, 193.9. HRMS (ESI-TOF, *m/z*): found 319.0326 ($[M+H]^+$, $C_{16}H_{16}BrO_2^+$; calc. 319.0328).

2-Bromo-2-phenyl-1-(thiophen-2-yl)ethan-1-one **12d.**

11d (0.303 g, 1.5 mmol), NBS (0.320 g, 1.8 mmol). Column chromatography on silica gel ($R_f = 0.53$, CH_2Cl_2/hexane 1:2 → 2:1). Yellow solid (0.304 g, 72%). M.p. 36–39 °C. IR (neat): ν 3089, 1660, 1514, 1494, 1454, 1408, 1353, 1285, 1237, 1222, 1178, 1062, 948, 859, 719, 691, 634 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.20 (*s*, 1H), 7.11 (dd, $J = 3.9$, 4.8 Hz, 1H), 7.30–7.40 (*m*, 3H), 7.53–7.59 (*m*, 2H), 7.68 (dd, $J = 0.9$, 4.8 Hz, 1H), 7.76 (dd, $J = 0.9$, 3.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 51.4, 128.3, 129.0, 129.0, 129.2, 133.4, 135.2, 135.8, 140.6, 184.1. HRMS (ESI-TOF, *m/z*): found 280.9628 ($[M+H]^+$, $C_{12}H_{10}BrOS^+$; calc. 280.9630).

2,2-Dibromo-2-phenyl-1-(thiophen-2-yl)ethan-1-one **13d.**

11d (0.303 g, 1.5 mmol), NBS (0.320 g, 1.8 mmol). Column chromatography on silica gel ($R_f = 0.67$, CH_2Cl_2/hexane 1:2 → 2:1). Brownish solid (0.052 g, 16%). M.p. 65–69 °C. IR (neat): ν 3109, 2921, 1667, 1491, 1444, 1406, 1350, 1238, 1222, 1190, 1084, 1064, 961, 845, 801, 749, 722, 704, 689, 648 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.92 (dd, $J = 4.0$, 4.9 Hz, 1H), 7.30 (dd, $J = 1.1$, 4.0 Hz, 1H), 7.33–7.42 (m, 3H), 7.56 (dd, $J = 1.1$, 4.9 Hz, 1H), 7.66–7.71 (*m*, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 68.4, 127.3, 127.8, 128.8, 129.8, 135.1, 136.1, 136.3, 140.7, 180.1. HRMS (ESI-TOF, *m/z*): found 358.8727 ($[M+H]^+$, $C_{12}H_9Br_2OS^+$; calc. 358.8735).

2-Bromo-2,4-diphenyl-3-oxobutanenitrile **15.**

14 (0.071 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Column chromatography on silica gel ($R_f = 0.70$, CH_2Cl_2/petroleum ether 1:3 → 2:1). Yellowish oil (0.070 g, 75%). IR (neat): ν 2923, 1731, 1495, 1449, 1320, 1031, 1002, 705, 691, 646 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.99 (*d*, $J = 16.7$ Hz, 1H), 4.03 (*d*, $J = 16.7$ Hz, 1H), 7.01–7.06 (*m*, 2H), 7.22–7.29 (*m*, 3H), 7.43–7.48 (*m*, 3H), 7.62–7.68 (*m*, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 43.1, 54.1, 116.0, 127.5, 127.6, 128.6, 129.4, 129.5, 130.6, 131.3, 132.1, 190.9. HRMS (ESI-TOF, *m/z*): found 314.0173 ($[M+H]^+$, $C_{16}H_{13}BrNO^+$; calc. 314.0175).

2-Bromo-2-phenylacetonitrile **18.**

16 (0.048 g, 0.3 mmol), NBS (0.059 g, 0.33 mmol). Preparative TLC ($R_f = 0.35$, CH_2Cl_2/petroleum ether 1:3)

Yellowish oil (0.031 g, 53%). IR (neat): 2971, 1496, 1455, 1188, 1138, 971, 817, 763, 690, 653, 621 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.49 (*s*, 1H), 7.39–7.48 (*m*, 3H), 7.52–7.60 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.4, 116.2, 127.8, 129.5, 130.3, 133.5.

1-(3-bromo-4-methoxynaphthalen-1-yl)ethanone 21a.

19a (0.200 g, 1.0 mmol), NBS (0.356 g, 2.0 mmol). Column chromatography on silica gel (R_f = 0.24, CH_2Cl_2/hexane 1:2 → 2:1). Brownish solid (0.008 g, 3%). M.p. 36–39 °C. IR (neat): ν 2940, 2848, 1663, 1568, 1501, 1401, 1352, 1275, 1229, 1134, 1073, 1008, 974, 835, 759, 712, 675, 627 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.72 (*s*, 3H), 4.05 (*s*, 3H), 7.55–7.68 (*m*, 2H), 8.07 (*s*, 1H), 8.16–8.21 (*m*, 1H), 8.74–8.80 (*m*, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.7, 61.7, 110.8, 122.3, 126.6, 127.3, 128.6, 129.6, 131.1, 132.8, 133.6, 156.9, 199.6. HRMS (ESI-TOF, *m/z*): found 279.0013 ($[M+H]^+$, $C_{13}H_{12}BrO_2^+$; calc. 279.0015).

(3-Bromo-4-methoxynaphthalen-1-yl)(phenyl)methanone 21c.

19c (0.079 g, 0.3 mmol), NBS (0.117 g, 0.66 mmol). Column chromatography on silica gel (R_f = 0.67, CH_2Cl_2/petroleum ether 1:3 → 2:1). Yellowish solid (0.101 g, 99%). M.p. 81–84 °C. IR (neat): ν 2922, 1649, 1567, 1501, 1448, 1372, 1270, 1243, 1152, 1070, 1054, 1022, 963, 863, 832, 763, 710, 693, 670, 656, 613 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.08 (*s*, 3H), 7.45–7.51 (*m*, 2H), 7.51–7.56 (*m*, 1H), 7.57–7.65 (*m*, 2H), 7.71 (*s*, 1H), 7.84–7.89 (*m*, 2H), 8.08 (*d*, *J* = 8.5 Hz, 1H), 8.22 (*d*, *J* = 8.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 61.7, 111.1, 122.4, 126.2, 127.4, 127.8, 128.6, 129.4, 130.4, 131.8, 132.1, 133.5, 133.9, 137.9, 155.6, 196.1. HRMS (ESI-TOF, *m/z*): found 341.0170 ($[M+H]^+$, $C_{18}H_{14}BrO_2^+$; calc. 341.0172).

2-Bromo-1-(3-bromo-4-methoxynaphthalen-1-yl)ethanone 22a.

19a (0.200 g, 1.0 mmol), NBS (0.356 g, 2.0 mmol). Column chromatography on silica gel (R_f = 0.33, CH_2Cl_2/hexane 1:2 → 2:1). Brownish solid (0.007 g, 2%). M.p. 64–69 °C. IR (neat): ν 2934, 1686, 1566, 1503, 1373, 1265, 1213, 1165, 1124, 1089, 1074, 973, 908, 860, 836, 789, 761, 718, 701, 680, 639 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.07 (*s*, 3H), 4.53 (*s*, 2H), 7.60–7.70 (*m*, 2H), 8.07 (*s*, 1H), 8.19–8.23 (*m*, 1H), 8.62–8.67 (*m*, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.3, 61.8, 110.6, 122.5, 126.3, 127.7, 129.0, 129.7, 129.8, 131.6, 133.4, 157.7, 192.4. HRMS (ESI-TOF, *m/z*): found 356.9117 ($[M+H]^+$, $C_{13}H_{11}Br_2O_2^+$; calc. 356.9120).

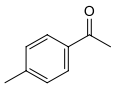
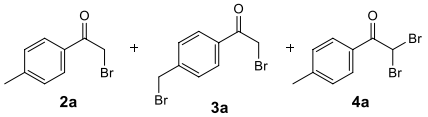
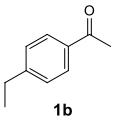
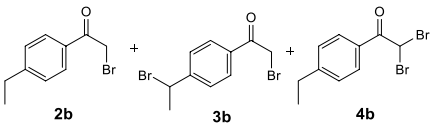
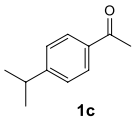
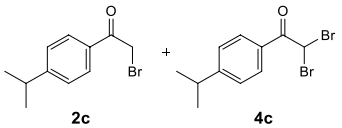
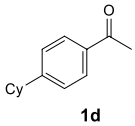
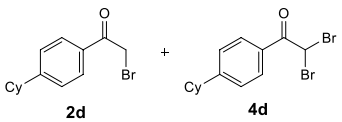
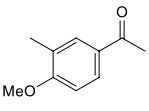
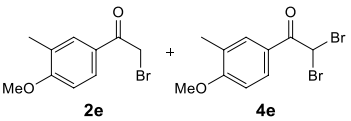
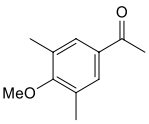
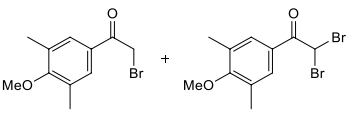
Results and discussion

The ketones under investigation were arranged into the groups of distinct alkyl substituents. First, we investigated the regioselectivity of functionalization at differently phenyl-functionalized model acetophenones **1a**–**f**. Neat ketones were reacted with NBS under stirring and irradiated using an 8-W energy-saving light bulb at 27 °C. The results are summarized in Table 1.

All substrates **1a–f** responded to the above reaction conditions in the same way, mainly affording α-bromoacetophenones **2a–f**, which were accompanied by α,α-dibrominated products **4a–f**. The selectivity was poorer in the cases of 4'-methylacetophenone **1a** and 4'-ethylacetophenone **1b**, where α-bromination was accompanied with benzylic bromination of the corresponding alkyl (Me and Et) group, resulting in a small amount of **3a** and **3b**, respectively (entries 1 and 2).

Surprisingly, selective benzylic bromination of 4'-methylacetophenone **1a** into 4'-bromomethylacetophenone took place with NBS in solvent-free reaction under concentrated solar radiation (Deshpande et al. 2015). A comparison of the photochemical functionalization of 4'-methylacetophenone **1a** with NBS under different reaction conditions revealed interesting features. On water, 4'-bromomethylacetophenone was the only product formed (Podgoršek et al. 2009), whereas the treatment of **1a** with NBS/$SiCl_4$ in MeCN furnished the compound **3a** as the sole product (Salama and Novák 2011). Conversely, compound **1a** was selectively α-brominated using NBS/PTSA under ultrasound irradiation in methanol (Adhikari and Samant, 2002). In contrast to the straight-chain functionalized derivatives, at the branched isopropyl **1c** and cyclohexyl **1d** acetophenones only α-bromination took place with no benzylic bromination observed (entries 4 and 5). Increasing the complexity of the substrate with additional reactive sites, e.g., in 3'-methyl-4'-methoxyacetophenone **1e** and 3',5'-dimethyl-4'-methoxyacetophenone **1f**, did not diminish the reaction selectivity, furnishing solely α-brominated ketones **2e/4e** and **2f/4f**, respectively (entries 6 and 8). Conducting the reactions with **1b** and **1e** in the presence of a radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxy) strongly influenced the selectivity outcome. As indicated in entries 3 and 7, benzylic bromination and introduction of the second bromine atom to the α-position were completely suppressed; hence, the only products formed were **2b** and **2e**, respectively. Transformation of **1f** did not take place in the absence of light (entry 9).

Table 1 Transformation of neat substituted acetophenones **1a–f** with NBS under visible-light irradiation

Entry	Substrate	Reaction conditions[a]	Products	Conv. [%][b]	Selectivity[b]
1	 **1a**	*hv*, 24h	 **2a** + **3a** + **4a**	100	**2a**, 52 (13) **3a**, 10 (4) **4a**, 38 (26)
2	 **1b**	*hv*, 29h	 **2b** + **3b** + **4b**	76	**2b**, 60 (15) **3b**, 24 (4) **4b**, 16[d]
3		*hv*, TEMPO[c], 24h		20	**2b**, 100[d]
4	 **1c**	*hv*, 21h	 **2c** + **4c**	78	**2c**, 66 (39) **4c**, 34 (21)
5	 **1d**	*hv*, 22h	 **2d** + **4d**	70	**2d**, 89 (36) **4d**, 11 (5)
6	 **1e**	*hv*, 24h	 **2e** + **4e**	81	**2e**, 56 (18) **4e**, 44 (29)
7		*hv*, TEMPO[c], 24h		11	**2e**, 100[d]
8	 **1f**	*hv*, 27h	 **2f** + **4f**	71	**2f**, 55 (19) **4f**, 45 (25)
9		dark, 21h		0	–

[a]Substrate **1** (0.3 mmol), NBS (0.33 mmol), stirring, 8-W energy-saving light bulb, reaction temperature 27 °C

[b]Conversions and relative distribution of products determined by ^{1}H NMR spectroscopy of the crude reaction mixtures; values in parentheses refer to isolated yields

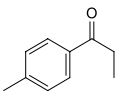
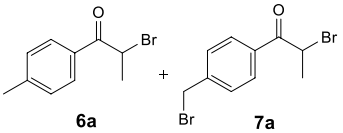
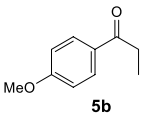
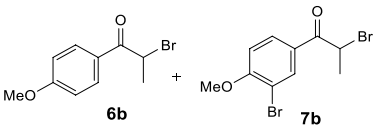
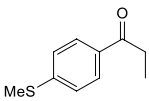
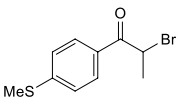
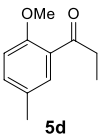
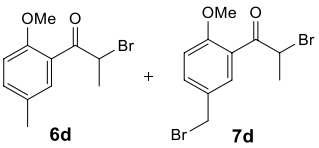
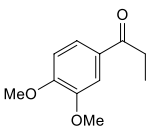
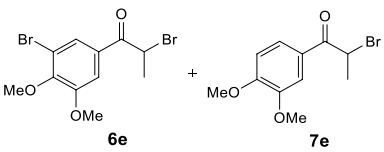
[c]TEMPO (0.3 equiv.) was added

[d]Products not isolated

Next, the selectivity of photo-transformations of model aryl-substituted propiophenones **5** with NBS under SFRC was examined. As with acetophenones **1**, α-bromination was the main reaction pathway, but in this case no α,α-dibrominated products could be detected. Transformations of most of the propiophenones exhibited a somewhat different selectivity compared to acetophenones. The results are summarized in Table 2.

Functionalization of 4'-methylpropiophenone **5a** yielded α-brominated ketone **6a** as the main product, accompanied with a product of mixed α- and benzylic bromination **7a** (entry 1). Benzylic bromination of **5a** in the presence of TEMPO was completely suppressed, and only α-bromination could be detected with low conversion into **6a** (entry 2). This might indicate that the main reaction channels are of a radical nature. The reaction of **5a** did not occur in the dark (entry 3). Transformation of 4'-methoxypropiophenone **5b** gave the corresponding α-bromoketone **6b** as the main product. To some extent, this was further brominated at the aromatic ring also yielding a minor product **7b** (entry 4). The sulfur analogue, 4'-methylthiopropiophenone **5c**, exhibited the highest selectivity with only the α-carbon atom being brominated, producing **6c** (entry 5). Unexpectedly, the methylthio group did not affect the type of functionalization as no aromatic

Table 2 Regioselectivity of functionalization of neat substituted propiophenones with NBS under visible light

Entry	Substrate	Reaction conditions[a]	Products	Conv. [%][b]	Selectivity[b]
1	 **5a**	*hv*, 27h	 **6a** + **7a**	87	**6a**, 61 (30) **7a**, 39 (20)
2		*hv*, TEMPO[c], 24h		25	**6a**, 100[e]
3		dark, 21h		0	–
4	 **5b**	*hv*, 23h[d]	 **6b** + **7b**	92	**6b**, 90 (68) **7b**, 10[e]
5	 **5c**	*hv*, 20h	 **6c**	83	100 (68)
6	 **5d**	*hv*, 19h	 **6d** + **7d**	98	**6d**, 93 (73) **7d**, 7[e]
7	 **5e**	*hv*, 24h	 **6e** + **7e**	90	**6e**, 90 (42) **7e**, 10[e]
8		*hv*, TEMPO[c], 24h		0	–

[a]Substrate **5** (0.3 mmol), NBS (0.33 mmol), stirring, 8-W energy-saving light bulb, reaction temperature 27 °C

[b]Conversions and relative distribution of products determined by ^{1}H NMR spectroscopy of the crude reaction mixtures; values in parentheses refer to isolated yields

[c]TEMPO (0.3 equiv.) was added

[d]Ketone (1.0 mmol), NBS (1.5 mmol)

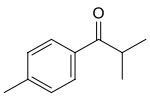
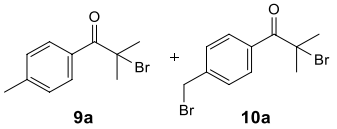
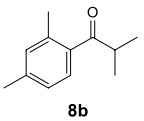
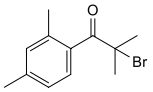
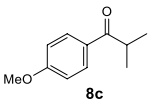
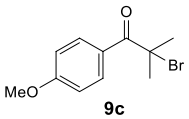
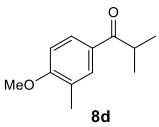
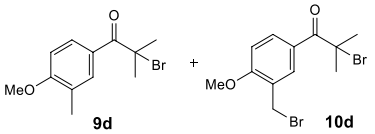
[e]Products not isolated

substitution took place. The sulfur atom, being itself sensitive to oxidation (Ali et al. 2006), remained unchanged. The reaction of 2'-methoxy-5'-methylpropiophenone **5d**, which contained at least three potential reactive sites, gave the related α-bromoketone **6d** as the main product as well as an additional side-chain brominated minor product **7d** (entry 6). Functionalization of 3',4'-dimethoxypropiophenone **5e** yielded α- and ring brominated **6e** as the main product, accompanied by 10% of α-bromoketone **7e** (entry 7). Interestingly, no reaction took place in the presence of TEMPO to **5e** (entry 8). It appears that aromatic substitution of **5e** takes place via a radical pathway. Reactions of α-bromination of acetophenones and propiophenones in the presence of TEMPO suggest involvement of electrophilic and radical reaction pathways without clear boundary.

Subsequently, we selected model isobutyrophenones (aryl isopropyl ketones) (Table 3).

In the group of acetophenones **1**, the isopropyl and cyclohexyl moieties in **1c** and **1d** did not undergo benzylic bromination (Table 1, entries 4 and 5). In this step, the reactivity of model isopropyl ketones was examined. The general feature of ketones **8** was that, regardless of the nature of the substituents under the studied reaction conditions, α-bromoketones **9** were formed as the main products. Functionalization of 4'-methylbutyrophenone **8a** in addition to the α-brominated ketone **9a** also leads to the formation of benzyl bromide **10a** (entry 1). The reaction of **8a** was completely suppressed in the presence of TEMPO (entry 2) as well as in the dark (entry 3). Reaction of 2',4'-dimethylisobutyrophenone **8b**, although being similar to **8a**, did not result in benzylic bromination, but the only product formed was α-bromoketone **9b** (entry 4). Transformation of 4'-methoxyisobutyrophenone **8c** exclusively produced α-bromoketone **9c** with no ring substitution noted (entry 5). The reaction of 3'-methyl-4'-methoxybutyrophenone **8d** furnished a mixture of α-bromoketone **9d** and benzyl bromide **10d** (entry 6). The addition of TEMPO to the reaction mixture resulted in the recovery of the starting material **8d**

Table 3 Regioselectivity of functionalization of neat substituted isobutyrophenones with NBS under visible light

Entry	Substrate	Reaction conditions[a]	Products	Conv. [%][b]	Selectivity[b]
1	 **8a**	*hv*, 21h	 **9a** **10a**	83	**9a**, 61 (23) **10a**, 39 (23)
2		*hv*, TEMPO[c], 24h		0	–
3		dark, 21h		0	–
4	 **8b**	*hv*, 24h	 **9b**	92	100 (53)
5	 **8c**	*hv*, 20h	 **9c**	91	100 (78)
6	 **8d**	*hv*, 20h[d]	 **9d** **10d**	78	**9d**, 69 (16) **10d**, 31 (18)
7		*hv*, TEMPO[c], 24h		0	–

[a]Substrate **8** (0.3 mmol), NBS (0.33 mmol), stirring, 8-W energy-saving light bulb, reaction temperature 27 °C

[b]Conversions and relative distribution of products determined by ^{1}H NMR spectroscopy of the crude reaction mixtures; values in parentheses refer to isolated yields

[c]TEMPO (0.3 equiv.) was added

[d]Ketone (1.0 mmol), NBS (1.5 mmol)

(entry 7). In contrast to acetophenones and propiophenones, the results of functionalization of isobutyrophenone suggest that α-bromination proceeds exclusively by a radical mechanism. This suggests that functionalization under solvent-free conditions might depend on substrate structure, reminiscent of radical α-bromination of highly substituted ketones with bromine in the presence of 1,2-epoxycyclohexane under photochemical conditions (Caló et al. 1977). Photochemical α-bromination of ketones with NBS under UV–Vis irradiation in diethyl ether is believed to follow a radical pathway (Arbuj et al. 2007).

In the next step, we explored the reactivity of the selected model benzyl ketones **11** (Table 4).

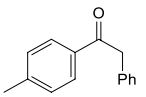
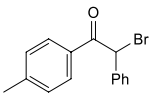
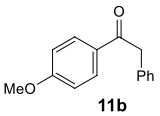
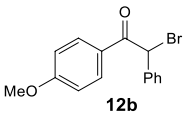
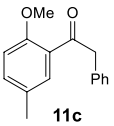
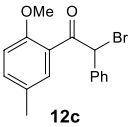
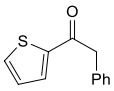
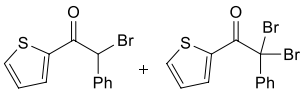
The highest regioselectivity was observed for this group, with all substrates being brominated at the carbonyl carbon atom. This outcome was anticipated, because the site of functionalization was an α-carbonyl and a benzylic position at the same time. The presence of either methyl group **11a**, methoxy group **11b** or both **11c** in the substrate did not influence the selectivity (entries 1, 3 and 4). Also, for the substrate with a sensitive thiophene ring like in **11d**, only α-bromination into **12d** was noticed, even though some α,α-dibrominated product **13d** was formed as well (entry 6). TEMPO completely stopped any transformation for **11a** and **11d** (entries 2 and 7), and no reaction took place for **11c** in the dark (entry 5). Functionalization of benzyl ketones in the presence of TEMPO indicates that α-bromination might proceed via radical pathway.

To examine the effect of the structure at the carbonyl group on the reactivity of transformations under the applied reaction conditions, two substrates, **14** and **16**, with an additional electron-withdrawing nitrile group bonded to one of the α-carbon atoms, were selected (Table 5).

Clearly, this triple activation in **14** and **16** had a strong influence on regioselectivity and the reaction afforded exclusively products **15** and **17**, respectively (entries 1 and 3). Both reactions of **14** and **16** occurred even in the dark (entries 2 and 4). When purifying the product **17** by means of column chromatography, we observed an interesting phenomenon, in which the acetyl group was partly cleaved on the column and a mixture of **17** and **18** was eluted. Attempts to separate these two compounds by a preparative thin-layer chromatography resulted in complete deacetylation of **17** into product **18**.

Finally, the reactivity of naphthyl ketones was examined (Table 6). The most interesting and unexpected result was

Table 4 Regioselectivity of functionalization of neat substituted benzyl ketones with NBS under visible light

Entry	Substrate	Reaction conditions[a]	Products	Conv. [%][b]	Selectivity[b]
1	 **11a**	*hv*, 24h	 **12a**	75	100 (35)
2		*hv*, TEMPO[c], 24h		0	–
3	 **11b**	*hv*, 24h	 **12b**	68	100 (60)
4	 **11c**	*hv*, 22h[d]	 **12c**	90	100 (63)
5		dark, 21h		0	–
6	 **11d**	*hv*, 22h[e]	 **12d** **13d**	100	**12d**, 80 (72) **13d**, 20 (16)
7		*hv*, TEMPO[c], 24h		0	–

[a]Substrate **11** (0.3 mmol), NBS (0.33 mmol), stirring, 8-W energy-saving light bulb, reaction temperature 27 °C

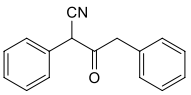
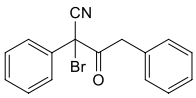
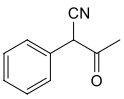
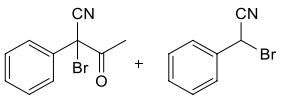
[b]Conversions and relative distribution of products determined by ^{1}H NMR spectroscopy of the crude reaction mixtures; values in parentheses refer to isolated yields

[c]TEMPO (0.3 equiv.) was added

[d]Ketone (0.5 mmol), NBS (0.6 mmol)

[e]Ketone (1.5 mmol), NBS (1.8 mmol)

Table 5 Regioselectivity of functionalization of neat substituted α-cyanoketones with NBS under visible light

Entry	Substrate	Reaction conditions[a]	Products	Conv. [%][b]	Selectivity[b]
1	 **14**	*hv*, 24h	 **15**	95	100 (75)
2		dark, 21h		95	100[d]
3	 **16**	*hv*, 24h	 **17** **18**	100	**17**, 100 (0) **18**, 0 (53)[c]
4		dark, 21h		100	**17**, 100[d]

[a]Substrate **14/16** (0.3 mmol), NBS (0.33 mmol), stirring, 8-W energy-saving light bulb, reaction temperature 27 °C

[b]Conversions and relative distribution of products determined by ^{1}H NMR spectroscopy of the crude reaction mixtures; values in parentheses refer to isolated yields

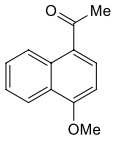
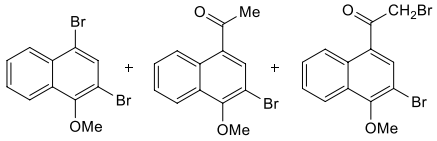
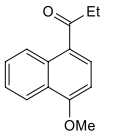
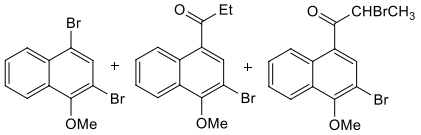
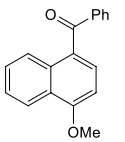
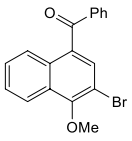
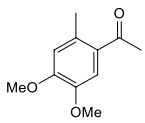
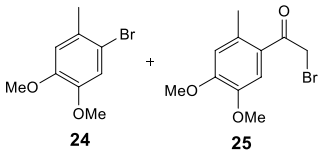
[c]Only **18** isolated after column and preparative chromatography

[d]Products not isolated

observed by irradiating (4-methoxynaphthyl) methyl ketone **19a** with 2.2 equiv. of NBS under SFRC.

Instead of the anticipated bromination at the alkyl side chain, the main reaction pathway was *ipso*-substitution of the acetyl group by a bromine atom alongside with aromatic and α-carbonyl bromination as minor pathways (entry 1). This observation stimulated us to examine the influence of the acyl moiety structure of (4-methoxynaphthyl) alkyl ketones on potential bromodeacylation. The fact that a similar distribution of the products was found for (4-methoxynaphthyl) ethyl ketone **19b** (entry 4) indicates that the *ipso*-substitution under these conditions could be more general. Although the illumination of (4-methoxynaphthyl) benzyl ketone resulted in a complex mixture of products, a significant amount of **20** was found in the crude reaction mixture, indicating that bromodeacylation occurs with NBS under

Table 6 Regioselectivity of functionalization of neat substituted naphthyl ketones with NBS under visible light

Entry	Substrate	Reaction conditions[a]	Products	Conv. [%][b]	Selectivity[b]
1	 **19a**	*hv*, 20h	 **20** **21a** **22a**	100	**20**, 91 (79) **21a**, 5 (3) **22a**, 4 (2)
2		*hv*, TEMPO[c], 24h		72	**20**, 88[f] **21a**, 12[f]
3		dark, 21h		<100[e]	Complex mixture[e]
4	 **19b**	*hv*, 24h	 **20** **21b** **22b**	100	**20**, 89 (72) **21b**, 7[f] **22b**, 4[f]
5	 **19c**	*hv*, 28h	 **21c**	99	100 (99)
6		*hv*, TEMPO[c], 24h		66	100
7		dark, 21h		0	–
8	 **23**	*hv*, 24h[d]	 **24** **25**	100	**24**, 89 (61) **25**, 11[f]
9		*hv*, TEMPO[c], 24h[d]		0	–

[a]Substrate **19** (0.3 mmol), NBS (0.66 mmol), stirring, 8-W energy-saving light bulb, reaction temperature 27 °C

[b]Conversions and relative distribution of products determined by ^{1}H NMR spectroscopy of the crude reaction mixtures; values in parentheses refer to isolated yields

[c]TEMPO (0.3 equiv.) was added

[d]Substrate **23** (0.3 mmol), NBS (0.33 mmol)

[e]Incomplete conversion, a complex reaction mixture

[f]Products not isolated

SFRC with this substrate as well. To test the hypothesis that an enolizable carbonyl group must be present for the *ipso*-substitution, the non-enolizable (4-methoxynaphthalen-1-yl)(phenyl)methanone **19c** was subjected to the same reaction conditions. The reaction exclusively furnished the ring-brominated product **21c** with no deacylation observed (entry 5). Interestingly, *ipso*-substitution was also noticed in the case of the considerably electron-rich aryl ketone 2'-methyl-4',5'-dimethoxyacetophenone **23**, in which the main bromodeacylated product **24** was accompanied by a small amount of α-bromoketone **25** (entry 8). Bromodeacylation is rather a rare process, known to take place with molecular bromine in a solution (Beirne et al. 1970). The addition of TEMPO to the reaction mixture resulted in different effects for different substrates. While inhibiting α-carbonyl bromination, it had no effect on *ipso*- and ring substitution at **19a** and **19c** (entries 2 and 6). In contrast, TEMPO completely suppressed all transformations of the compound **23** (entry 9). Selectivity of the transformation of **19a** in the dark was decreased considerably resulting in a complex mixture of products (entry 3), while no reaction took place with **19c** in the absence of light (entry 7).

Some further experiments were carried out in order to shed light on mechanism of bromodeacylation. 4-Methoxy-1-acetonaphthone **19a** was reacted as a model substrate under different reaction conditions with NBS and bromine. Transformation of **19a** with NBS/NH_4OAc in diethyl ether (Tanemura et al. 2004) led to 2-bromo-1-(4-methoxynaphthalen-1-yl)ethan-1-one with 35% conversion. Reaction of **19a** with NBS/NH_4NO_3 in acetonitrile (Tanemura et al. 2003) furnished a complex mixture of ring-brominated products and a small proportion of

bromodeacylated product **20**. Functionalization of **19a** with bromine in acetic acid furnished 2-bromo-1-(4-methoxynaphthalen-1-yl)ethan-1-one with 65% conversion. This reaction is assumed to take place in an electrophilic fashion via enol form of **19a**. The system NBS/*p*TSA in DCM (Pravst et al. 2008; Vyas et al. 2016) expectedly furnished 2-bromo-1-(4-methoxynaphthalen-1-yl)ethan-1-one with 80% conversion. It can be concluded that electrophilic functionalization of α-carbonyl position takes place in the present of an acid (Br_2/AcOH and NBS/*p*TSA in DCM). The system NBS/NH_4NO_3 in acetonitrile led to the expected electrophilic ring functionalization; in addition, a minor portion of *ipso*-product **20** was observed. Reactions in the presence of TEMPO suggest that the ring functionalization of **19a** might proceed via electrophilic and radical reaction pathways, while formation of **20** is supposed to be attributed to a different reaction channel—potentially a radical ion reaction pathway (Fasani et al. 1994).

Conclusions

In this study, we disclosed regioselectivity of visible-light-induced transformations of model aryl methyl-, aryl ethyl-, aryl isopropyl-, aryl benzyl-, α-cyano-substituted- and naphthyl alkyl ketones, containing several competitive reactive sites with NBS in the absence of solvents. The entire study was carried out under heterogeneous reaction conditions. In most cases, α-brominated ketones were the main products, accompanied with α,α-dibrominated ketones. Wohl–Ziegler bromination and aromatic ring bromination were noted as minor reaction pathways in the case of several alkyl- and alkoxy-substituted ketones. The α-bromination of ketones under solvent-free reaction conditions appears to depend on the structure of the substrates. While in the case of acetophenones and propiophenones it is proposed to proceed by the electrophilic and radical pathways, in the case of isobutyrophenones and aryl benzyl ketones it is likely to take place by the radical pathway. α-Cyano-substituted ketones were converted into their α-bromo-α-cyano-substituted derivatives even in the dark. An unexpected exception was the reaction of enolizable (4-methoxynaphthyl) alkyl ketones, in which the main product was formed because of an *ipso*-substitution of the acyl group with a bromine atom. Bromodeacylation is suggested to proceed via a radical cation intermediates. The radical scavenger TEMPO slowed or suppressed α- and ring bromination, whereas benzylic bromination and α,α-dibromination with NBS were entirely suppressed. It was demonstrated in several cases that reactions might proceed in electrophilic and radical fashion without a distinct boundary. In summary, we contributed to understanding reaction pathways of these sensitive compounds in reactions with NBS under solvent-free reaction conditions.

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