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ORIGINAL PAPER

Isoquinoline-catalyzed addition of 2-bromo-1-aryl-1-ethanone to dialkyl azodicarboxylate: synthesis of trialkyl 2-[(1*E*)-*N*-(alkoxycarbonyl)-2-aryl-2-oxoethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate

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Abstract A catalytic method for the synthesis of a class of hydrazine derivatives is reported. The described method provides convenient access to compounds which are anticipated to show biological activities. The salient features of this process include operational simplicity, good yields, and easily accessible starting materials.

Keywords Ylides · Diazo compounds · Amines · Catalysis

Introduction

Hydrazine derivatives are currently of considerable technical and commercial importance; they are used in the pharmaceutical, agrochemical, polymer, and dye industries, and as precursors in organic synthesis [1–3]. Hydrazines have found applications in a large number of areas. Many of them show remarkable biological activities and various similar compounds have been shown to be effective for the treatment of hypertension, tuberculosis, and Parkinson's disease [1–3]. Some hydrazines display neuroprotective properties and are used as antidepressant drugs [4]. Hydrazine-based peptidomimetics (aza-peptides) were found to be potent agents against hepatitis [5], AIDS [6], and SARS [7]. For example, isoniazide (**1**) is the mainstay of antituberculosis therapy. The tubercle bacilli lose their acid-fastness and viability when exposed to isoniazide [8–10]. Compound **2**, known as Rh-5849, has been found to have commercial-level activity against a range of insect pest species, whereas—most importantly—it was judged to have a benign ecotoxicological profile and be nontoxic to beneficial insect species. Compound **3**, which is a chlorinated derivative of **2**, has been found to mimic the action of 20-hydroxyecdysone in insects. Two other analogs, tebufenozide (**4**) and halofenozide (**5**), known as Rh-5992 and Rh-6345, respectively, show similar activities and exhibit high specific toxicity to non-lepidopteran species [1–3, 7]. Iproniazid (**6**) and phenelzine (**7**) are used as antidepressants with monoamine-oxidase inhibitory effects, and hydralazine (**8**) is used as an antihypertensive drug [11] (Fig. 1). As a result of considerable interest in substituted hydrazines, the synthesis of hydrazine derivatives is a matter of significant interest from both theoretical and practical perspectives [12–15].

Monosubstituted hydrazines can be prepared by hydrazine alkylation, by reducing C=N bonds of hydrazones, or by direct amination and amination via diaziridines [16, 17]. 1,1- and 1,2-disubstituted hydrazines can be prepared by alkylation of free or suitably substituted hydrazines or via the reduction of *N*-nitroso secondary amines or hydrazones and hydrazides. Tri- and tetrasubstituted hydrazines are also prepared by similar alkylation and reduction processes. However, the alkylation of hydrazines is difficult to control and generally produces mixtures containing higher alkylated products [16, 17].

Conjugate addition to azodicarboxylates is one of the preferred methods of electrophilic amination, and has been used in the preparation of hydrazines [18–20]. Several groups have presented the direct amination of active methine compounds such as aldehydes [21–23], ketones

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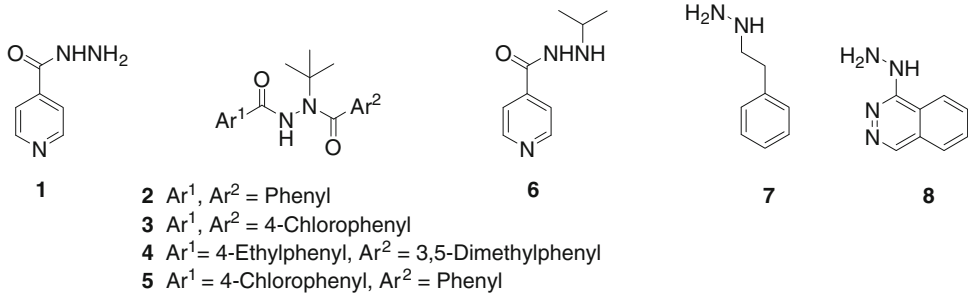
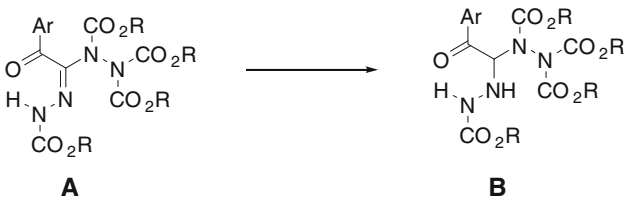
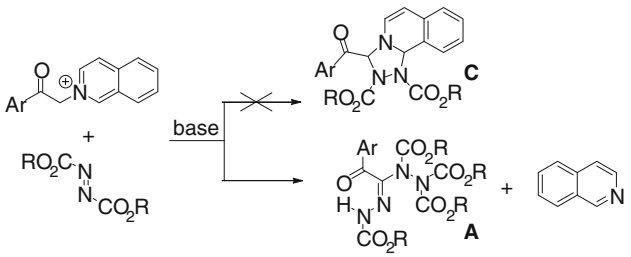


Fig. 1 Structures of some biologically active hydrazine derivatives



Scheme 1



Scheme 2

[24], β-ketoesters [25–34], β-ketophosphonates [35, 36], α-cyanoacetates [37], and α-cyanoketones [38–40] in the presence of metal complexes or organocatalysts. Other methods of amination using sources of electrophilic nitrogen including sulfonyl azides [41], sulfonyloxycarbamates [42], 1-chloro-1-nitroso reagents [43], and oxaziridines [44] have also been developed.

Results and discussion

In this work we would like to report an efficient procedure for the synthesis of a class of hydrazines with structure **A**, which contains both hydrazone and hydrazine functionalities. Compound **A** can be readily reduced to hydrazine **B** (Scheme 1).

As hydrazine derivatives with similar structures have been shown to have biological activities, it is expected that the abovementioned derivatives of hydrazine will also show interesting pharmacological effects.

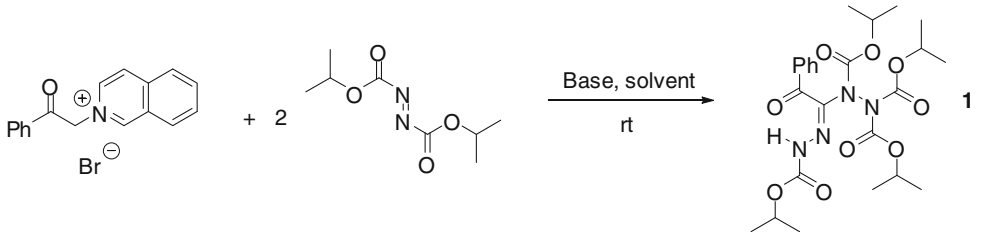
Ylide research has evolved in recent years, and ylides are now powerful and versatile synthetic tools in organic chemistry [45–48]. As a part of our current studies on the development of efficient methods for the preparation of heterocyclic compounds using ylide chemistry [49–51], we investigated the reaction of nitrogen ylides (prepared by the reaction of phenacyl bromide derivatives and isoquinoline) with dialkyl azodicarboxylates, in order to consider the possibility of forming **C** via a cyclization reaction. As Scheme 2 shows, the reaction led to the formation of **A** along with the liberation of isoquinoline.

To explore the scope and versatility of this procedure, we first investigated the effects of solvent and temperature on the reaction. Table 1 shows that the reaction using CH_2Cl_2 as the solvent and K_2CO_3 as the base gave the best results at room temperature.

Based on the above results and the previous report by Jones et al. [52], we turned our attention to investigating the isoquinoline-catalyzed addition of phenacyl bromides to dialkyl azodicarboxylate (Table 2). At first we examined the reaction of phenacyl bromide with diisopropyl diazodicarboxylate in the presence of a catalytic amount of isoquinoline (15 mol%), K_2CO_3 as the base, and CH_2Cl_2 as the solvent at room temperature (Table 2, entry 1). Despite the increased reaction time (24 h), the reaction led to the desired product in good yield. To reduce the reaction time, the reaction was carried out in CH_3CN under reflux conditions, and it had completed after 3 h. The reaction was also monitored with different catalyst loadings. At lower catalyst loadings (10 and 5 mol%), the reaction took longer and did not complete, even after stirring for 48 h. Also, to consider the influence of the ylide type (an intermediate formed during the reaction), the reactions of other nitrogen, phosphorus, and arsine ylides were investigated under the abovementioned reaction conditions. The results are summarized in Table 2.

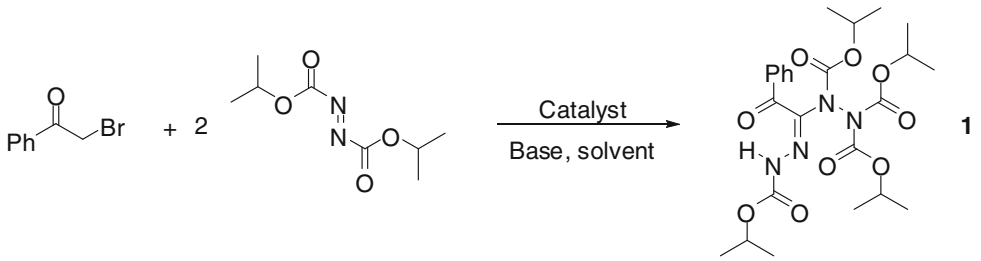
As the results in Table 2 show, the catalyst is of crucial importance, and the best result for the formation of **1** was obtained in the presence of isoquinoline. Pyridine, triphenylphosphine, and DABCO mainly led to the formation of a 1:1 adduct of phenacyl bromide and dialkyl azodicarboxylate. When the optimized conditions were used, the reactions of various phenacyl bromides with alkyl azodicarboxylates afforded good yields of trialkyl 2-[(1*E*)-*N*-(alkoxycarbonyl)-2-aryl-2-oxoethanehydrazonoyl]hydrazine-1,1,2-tricarboxylates (Table 3). Finally, to further

Table 1 The effects of the base and solvent on the reaction of the isoquinolinium salt of phenacyl bromide with diisopropyl azodicarboxylate



Entry	Base	Solvent	Time/h	Yield/%
1	KOH	CH_2Cl_2	8	83
2	**K_2CO_3**	**CH_2Cl_2**	**8**	**85**
3	Et_3N	CH_2Cl_2	10	<5
4	DBU	CH_2Cl_2	10	63
5	K_2CO_3	CH_3CN	8	78
6	K_2CO_3	THF	8	74
7	K_2CO_3	DMF	8	71

Table 2 The effects of the catalyst and the temperature on the reaction of phenacyl bromide with diisopropyl azodicarboxylate



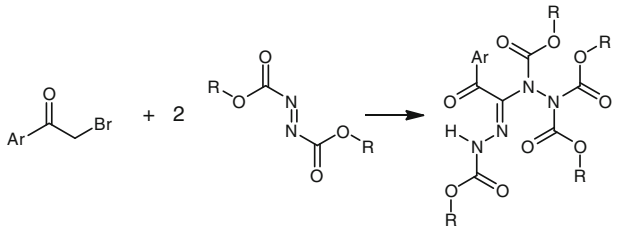
Entry	Catalyst	Temperature	Solvent	Time/h	Yield of **1**/%
1	Isoquinoline	rt	CH_2Cl_2	24	82
2	Isoquinoline	Reflux	CH_3CN	3	87
3	Pyridine	Reflux	CH_3CN	6	<5
4	*N*-Methylimidazole	Reflux	CH_3CN	3	64
5	DABCO	Reflux	CH_3CN	6	<5
6	Triphenylphosphine	Reflux	CH_3CN	6	<5
7	Triphenylarsine	Reflux	CH_3CN	6	<5

explore the potential of this protocol for the synthesis of this class of hydrazine derivatives, we investigated a reaction involving chloroacetonitrile and obtained triisopropyl 2-[(1*E*)-2-cyano-*N*-(isopropoxycarbonyl)-2-oxoethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate in moderate yield (Table 3, entry 14).

The structures of the products were characterized by spectroscopic analysis and further confirmed by the X-ray diffraction of **1** as a representative example (Fig. 2).

The ^{1}H NMR spectrum of **1** exhibited four doublet signals that were readily recognized as arising from isopropyl methyl groups at $\delta = 1.15$, 1.23, 1.37, and 1.38 ppm and isopropyl methine groups at $\delta = 4.83$, 4.95, and 5.16 ppm. Aromatic protons gave rise to characteristic signals in the aromatic region of the spectrum. The NH proton appeared at 8.51 ppm as a broad signal. The proton-decoupled ^{13}C NMR spectrum of **1** showed 16 distinct resonances, in agreement with the proposed

Table 3 Reactions of 2-bromoacetophenones with dialkyl azodicarboxylates under the optimized reaction conditions



1-14

Entry	Ar	R	Product	Yield / %
1	Ph	Pr^i	**1**	87
2	4-BrPh	Pr^i	**2**	73
3	4-MeOPh	Pr^i	**3**	65
4	4-PhPh	Pr^i	**4**	90
5	4-NO_2-Ph	Pr^i	**5**	85
6	4-ClPh	Pr^i	**6**	83
7	3-BrPh	Et	**7**	57
8	Ph	Et	**8**	76
9	4-PhPh	Et	**9**	81
10	4-ClPh	Et	**10**	80
11	4-MeOPh	Et	**11**	68
12	Ph	Bu^t	**12**	49
13	4-ClPh	Bu^t	**13**	53
14	ClMe	Pr^i	**14**	40

structure. The carbonyl group of **1** appears at $\delta =$ 185.5 ppm.

Although we have not established the mechanism of the reaction in an experimental manner, a possible explanation is shown in Scheme 3. The reaction of isoquinoline with phenacyl bromide derivatives leads to quaternary ammonium salt **D**. Deprotonation of **D** with K_2CO_3 forms the corresponding ylide, which would attack dialkyl azodicarboxylate in a Michael addition manner to yield the intermediate **E**. The intermediate **E** undergoes a 1,3-hydrogen shift to produce ylide **F**. The intermediate **F** adds to dialkyl azodicarboxylate to form **G**. The intramolecular rearrangement of **G**, via intermediate **H**, leads to the intermediate **I**, which can easily eliminate isoquinoline to afford the hydrazine **A**.

In conclusion, we have developed a catalytic and efficient methodology for the synthesis of trialkyl 2-[(1*E*)-*N*-(alkoxycarbonyl)-2-aryl-2-oxoethanehydrazonoyl]hydrazine-1,1,-2-tricarboxylate. Simplicity of operation, easily accessible starting materials, good yields, easy work-up, and the purification of compounds by a nonchromatographic method (crystallization only) are the key advantages of this method.

Experimental

All chemicals and solvents were purchased from Merck and used without further purification. Thin layer chromatography (TLC) analysis was performed using Silicycle precoated TLC plates (silica gel 60 F_{254}). The products were purified by preparative column chromatography on silica gel (0.063–0.200 mm; Merck). Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were measured on a Shimadzu FT-IR-4300 spectrometer. ^{1}H and ^{13}C NMR spectra (in $CDCl_3$) were measured with a Bruker Avance DRX-500 Advance (^{1}H NMR 500.1 MHz and ^{13}C NMR 125.7 MHz). Mass spectra were recorded on an HP 5973 GC–MS instrument operating at an ionization potential of 70 eV.

General procedure for the synthesis of triisopropyl-2-[(1E)-N-(isopropoxycarbonyl)-2-oxo-2-phenylethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate (**1**, $C_{24}H_{34}N_4O_9$)

Into a 25 cm^3 round bottom flask, phenacyl bromide (1 mmol) and diisopropyl azodicarboxylate (2 mmol) were added in the presence of 15 mol% of isoquinoline in 10 cm^3 acetonitrile. Then the reaction mixture was stirred under reflux for 3 h. The progress of the reaction was monitored by the fading of the yellow color and also by TLC. After the reaction had completed, the solvent was removed under reduced pressure, water was added, and the reaction mixture was extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4, and then the solvent was removed. Diethyl ether was added to the resulting oily crude product. It was cooled overnight and the precipitated solid formed was recrystallized from ethanol to obtain the pure product as yellow crystals (87%); m.p.: 122–124 °C; IR (KBr) $\bar{\nu} =$ 3,238, 2,937, 1,766, 1,730, 1,704, 1,681, 1,598, 1,481, 1,409, 1,367, 1,305, 1,232, 1,100, 1,020 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta =$ 1.15 (d, $J =$ 6.2 Hz, 6H), 1.23 (d, $J =$ 6.2 Hz, 6H), 1.37 (d, $J =$ 6.2 Hz, 6H), 1.38 (d, $J =$ 6.2 Hz, 6H), 4.83 (m, 1H), 4.95 (m, 1H), 5.16 (m, 2H), 7.51 (m, 2H), 7.62 (m, 1H), 8.19 (d, $J =$ 7.5 Hz, 2H), 8.51 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta =$ 22.0, 22.1, 22.2, 22.3, 70.1, 72.9, 73.0, 74.1, 129.1, 129.3, 134.6, 135.8, 150.8, 151.3, 153.2, 185.5 ppm; MS (EI, 70 eV): *m/z* (%) = 522 (2), 417 (6), 350 (6), 308 (4), 290 (5), 266 (9), 222 (17), 204 (20), 191 (8), 178 (25), 161 (15), 132 (17), 105 (100).

Triisopropyl 2-[(1E)-2-(4-bromophenyl)-N-(isopropoxycarbonyl)-2-oxoethanehydrazonoyl]-hydrazine-1,1,2-tricarboxylate (**2**, $C_{24}H_{33}BrN_4O_9$)
White solid (73%); m.p.: 142–143 °C; IR (KBr) $\bar{\nu} =$ 3,315, 2,985, 1,780, 1,728, 1,674, 1,587, 1,529, 1,377, 1,317, 1,290, 1,263, 1,226, 1,180, 1,099, 1,020 cm^{-1}; ^{1}H NMR

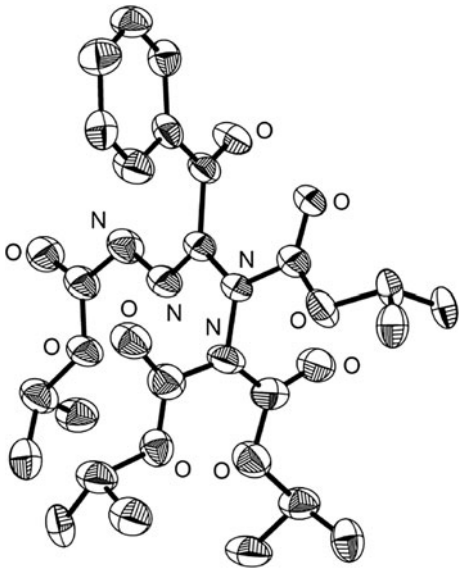


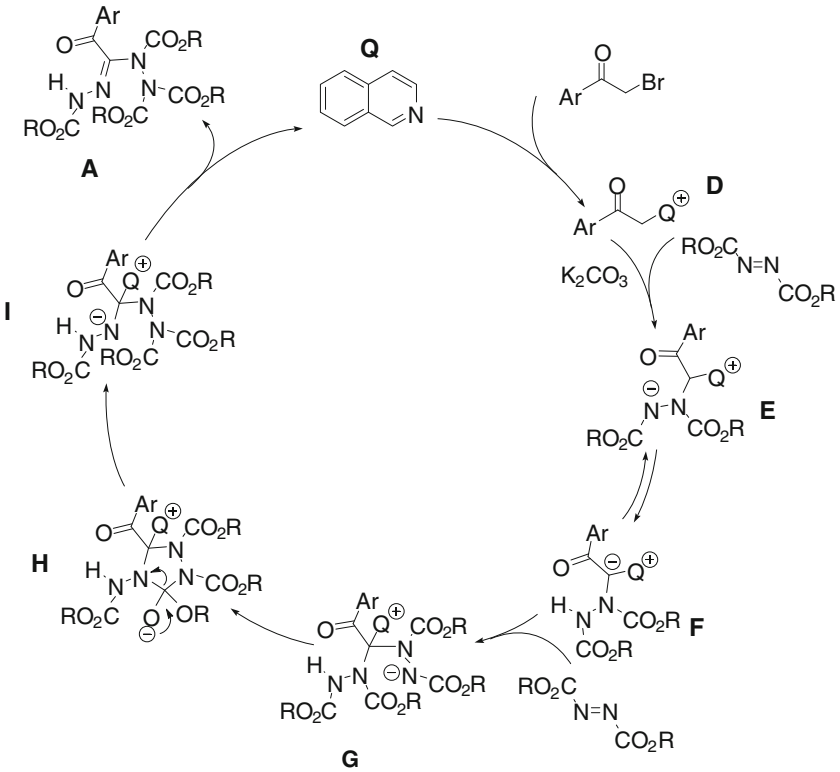
Fig. 2 X-ray crystal structure of **1**

(500.1 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J = 6.2$ Hz, 6H), 1.26 (d, $J = 6.2$ Hz, 6H), 1.40 (t, $J = 6.2$ Hz, 12H), 4.85 (m, 1H), 5.00 (m, 1H), 5.17 (m, 2H), 7.67 (d, $J = 8.3$ Hz, 2H), 8.30 (d, $J = 8.3$ Hz, 2H), 8.69 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 22.0$, 22.1, 22.2, 22.3, 70.2, 73.13, 74.2, 129.9, 130.6, 132.7, 134.8, 150.9, 153.3, 184.4 ppm; MS (EI, 70 eV): *m/z* (%) = 602 (M^+, ^{81}Br, 3), 600 (M^+, ^{79}Br, 3), 500 (3), 457 (1), 443 (1), 430 (7), 417 (20), 344 (20), 300 (20), 284 (27), 256 (29), 212 (20), 185 (100), 155 (17), 106 (27).

Triisopropyl 2-[(1E)-N-(isopropoxycarbonyl)-2-(4-methoxyphenyl)-2-oxoethanehydrazonoyl]-hydrazine-1,1,2-tricarboxylate (**3**, $C_{25}H_{36}N_4O_{10}$)
Greenish white solid (65%); m.p.: 124–126 °C; IR (KBr) $\bar{\nu}$ = 3,421, 2,987, 1,770, 1,735, 1,664, 1,596, 1,514, 1,375, 1,263, 1,228, 1,180, 1,097, 1,024, 937 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J = 6.2$ Hz, 6H), 1.23 (d, $J = 6.2$ Hz, 6H), 1.38 (d, $J = 6.2$ Hz, 6H), 1.39 (d, $J = 6.2$ Hz, 6H), 3.90 (s, 3H), 4.87 (m, 1H), 4.96 (m, 1H), 5.15 (m, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 8.21 (d, $J = 8.6$ Hz, 2H), 8.35 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 22.0$, 22.1, 22.2, 22.3, 56.0, 69.9, 72.8, 72.9, 73.9, 114.7, 128.6, 131.8, 132.5, 150.8, 151.3, 153.0, 165.0, 184.1 ppm; MS (EI, 70 eV): *m/z* (%) = 552 (3), 417 (6), 380 (3), 320 (3), 294 (4), 252 (6), 234 (20), 208 (15), 162 (22), 135 (100).

Triisopropyl 2-[(1E)-2-(biphenyl-4-yl)-N-(isopropoxycarbonyl)-2-oxoethanehydrazonoyl]-hydrazine-1,1,2-tricarboxylate (**4**, $C_{30}H_{38}N_4O_9$)
Yellow solid (90%); m.p.: 137–138 °C; IR (KBr) $\bar{\nu}$ = 3,421, 2,935, 1,770, 1,735, 1,672, 1,604, 1,523, 1,375, 1,261, 1,226, 1,180, 1,093 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.20$ (d, $J = 6.2$ Hz, 6H), 1.27 (d, $J = 6.2$ Hz, 6H), 1.42 (d, $J = 6.2$ Hz, 6H), 1.43 (d,

Scheme 3



$J = 6.2$ Hz, 6H), 4.89 (m, 1H), 5.00 (m, 1H), 5.20 (m, 2H), 7.46 (m, 1H), 7.52 (t, $J = 7.3$ Hz, 2H), 7.67 (d, $J = 7.3$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 2H), 8.32 (d, $J = 8.0$ Hz, 2H), 8.54 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 22.0$, 22.1, 22.2, 22.3, 70.1, 72.9, 73.0, 74.1, 127.7, 128.0, 128.9, 129.4, 129.8, 134.5, 140.1, 147.3, 150.8, 151.4, 151.9, 153.2, 185.1 ppm; MS (EI, 70 eV): *m/z* (%) = 598 (1), 417 (5), 366 (4), 340 (3), 322 (5), 298 (5), 280 (26), 254 (10), 208 (16), 181 (100), 152 (21).

Triisopropyl 2-[(1E)-N-(isopropoxycarbonyl)-2-(4-nitrophenyl)-2-oxoethanehydrazonoyl]-hydrazine-1,1,2-tricarboxylate (**5**, $C_{24}H_{33}N_5O_{11}$)
Greenish white solid (85%); m.p.: 157–159 °C; IR (KBr) $\bar{\nu} = 3{,}315$, 2,986, 1,776, 1,721, 1,682, 1,526, 1,375, 1,344, 1,221, 1,094 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.15$ (d, $J = 6.2$ Hz, 6H), 1.27 (d, $J = 6.2$ Hz, 6H), 1.40 (t, $J = 6.2$ Hz, 12H), 4.79 (m, 1H), 5.00 (m, 1H), 5.17 (m, 2H), 8.35 (d, $J = 8.7$ Hz, 2H), 8.45 (d, $J = 8.7$ Hz, 2H), 9.14 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 21.9$, 22.1, 22.14, 22.3, 70.4, 73.3, 73.3, 124.2, 129.9, 141.0, 150.8, 151.0, 153.7, 183.6 ppm; MS (EI, 70 eV): *m/z* (%) = 567 (1), 417 (3), 395 (3), 353(6), 324 (4), 311 (20), 267 (10), 249 (12), 223 (15), 177 (19), 150 (19).

Triisopropyl 2-[(1E)-2-(4-chlorophenyl)-N-(isopropoxycarbonyl)-2-oxoethanehydrazonoyl]-hydrazine-1,1,2-tricarboxylate (**6**, $C_{24}H_{33}ClN_4O_9$)
White solid (83%); m.p.: 140–142 °C; IR (KBr) $\bar{\nu} = 3{,}314$, 2,984, 1,775, 1,726, 1,675, 1,584, 1,524, 1,406, 1,374, 1,258, 1,221, 1,177, 1,094 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.18$ (d, $J = 6.2$ Hz, 6H), 1.26 (d, $J = 6.2$ Hz, 6H), 1.40 (t, $J = 6.2$ Hz, 12H), 4.85 (m, 1H), 4.99 (m, 1H), 5.16 (m, 2H), 7.59 (d, $J = 8.7$ Hz, 2H), 8.20 (d, $J = 8.7$ Hz, 2H), 8.6 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 22.0$, 22.1, 22.2, 22.3, 70.2, 73.0, 73.1, 74.2, 129.6, 130.5, 134.3, 141.0, 150.8, 153.3, 184.2 ppm; MS (EI, 70 eV): *m/z* (%) = 556 (1), 417 (14), 384 (9), 342 (8), 324 (7), 300 (22), 279 (11), 256 (25), 238 (22), 225 (9), 212 (30).

Triethyl 2-[(1E)-2-(3-bromophenyl)-N-(ethoxycarbonyl)-2-oxoethanehydrazonoyl]-hydrazine-1,1,2-tricarboxylate (**7**, $C_{20}H_{25}BrN_4O_9$)
Light yellow solid (57%); m.p.: 106–107 °C; IR (KBr) $\bar{\nu} = 3{,}622$, 3,281, 1,802, 1,726, 1,676, 1,513, 1,374, 1,225, 1,175, 1,083, 1,026 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.18$ (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.38 (t, $J = 7.2$ Hz, 6H), 4.14 (q, $J = 7.2$ Hz, 2H), 4.18 (q, $J = 7.2$ Hz, 2H), 4.22 (q, $J = 7.2$ Hz, 4H), 7.39 (t, $J = 7.8$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 8.15 (d, $J = 7.8$ Hz, 1H), 8.30 (s, 1H), 8.73 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.5$, 14.6, 14.8, 62.5, 64.8, 65.0, 123.5, 127.7, 130.9, 131.7, 137.4, 137.5, 151.2, 153.6, 184.0 ppm; MS (EI, 70 eV): *m/z* (%) = 546 (M^+, ^{81}Br, 2), 544 (M^+, ^{79}Br, 2), 430 (2), 384 (2), 361 (45), 325 (6), 297 (8), 284 (20), 269 (8), 212 (14), 185 (100), 157 (25), 129 (24).

Triethyl 2-[(1E)-N-(ethoxycarbonyl)-2-oxo-2-phenylethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate (**8**)
White solid (76%); m.p.: 100–101 °C (89–90 °C [52]).

Triethyl 2-[(1E)-2-(biphenyl-4-yl)-N-(ethoxycarbonyl)-2-oxoethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate (**9**, $C_{26}H_{30}N_4O_9$)
Yellow solid (81%); m.p.: 111–113 °C; IR (KBr) $\bar{\nu} = 3{,}141$, 2,910, 1,766, 1,750, 1,703, 1,677, 1,600, 1,488, 1,423, 1,373, 1,350, 1,247, 1,224, 1,093, 1,016, 972 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.17$ (t, $J = 7.0$ Hz, 3H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.39 (t, $J = 7.0$ Hz, 6H), 4.15 (m, 4H), 4.41 (q, $J = 7.0$ Hz, 4H), 7.40 (m, 1H), 7.47 (t, $J = 7.3$ Hz, 2H), 7.62 (d, $J = 7.3$ Hz, 2H), 7.72 (d, $J = 7.8$ Hz, 2H), 8.26 (d, $J = 7.8$ Hz, 2H), 8.54 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.4$, 14.5, 14.7, 62.3, 64.4, 64.8, 127.4, 127.6, 128.8, 129.3, 129.7, 134.3, 140.0, 147.3, 151.2, 151.7, 153.4, 153.6, 185.0 ppm; MS (EI, 70 eV): *m/z* (%) = 542 (7), 496 (10), 424 (5), 398 (2), 361 (16), 308 (5), 292 (4), 280 (18), 265 (5), 241 (4), 208 (10), 181 (100), 153 (27).

Triethyl 2-[(1E)-2-(4-chlorophenyl)-N-(ethoxycarbonyl)-2-oxoethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate (**10**, $C_{20}H_{25}ClN_4O_9$)
White solid (80%); m.p.: 137–139 °C; IR (KBr) $\bar{\nu} = 3{,}314$, 2,987, 1,757, 1,756, 1,674, 1,583, 1,522, 1,376, 1,338, 1,294, 1,208, 1,013, 751 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.17$ (t, $J = 7.0$ Hz, 3H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.39 (t, $J = 7.0$ Hz, 6H), 4.13 (q, $J = 7.0$ Hz, 2H), 4.18 (q, $J = 7.0$ Hz, 2H), 4.40 (q, $J = 7.0$ Hz, 4H), 7.47 (d, $J = 8.3$ Hz, 2H), 8.16 (d, $J = 8.3$ Hz, 2H), 8.72 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.4$, 14.5, 14.7, 62.4, 64.7, 64.9, 129.7, 130.5, 134.1, 141.0, 151.3, 151.7, 153.5, 184.2 ppm; MS (EI, 70 eV): *m/z* (%) = 500 (2), 379 (1), 361 (25), 310 (4), 281 (5), 266 (4), 253 (6), 238 (14), 225 (5), 166 (14), 139 (100), 111 (22).

Triethyl 2-[(1E)-N-(ethoxycarbonyl)-2-(4-methoxyphenyl)-2-oxoethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate (**11**, $C_{21}H_{28}N_4O_{10}$)
Yellow solid (68%); m.p.: 114–115 °C; IR (KBr) $\bar{\nu} = 3{,}280$, 2,981, 1,726, 1,658, 1,595, 1,507, 1,375, 1,259, 1,221, 1,164, 1,088, 1,019, 847 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.0$ Hz, 3H), 1.20 (t, $J = 7.0$ Hz, 3H), 1.29 (t, $J = 7.0$ Hz, 3H), 1.34 (t, $J = 7.0$ Hz, 3H), 4.13 (m, 4H), 4.36 (q, $J = 7.0$ Hz, 2H),

6.94 (d, $J = 8.0$ Hz, 2H), 8.22 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.3$, 14.5, 14.7, 55.9, 62.2, 64.5, 64.8, 65.5, 114.7, 129.0, 131.8, 151.2, 152.5, 153.2, 153.8, 165.1, 183.9 ppm; MS (EI, 70 eV): *m/z* (%) = 496 (1), 406 (4), 378 (4), 334 (19), 306 (9), 275 (4), 262 (31), 247 (13), 234 (21), 219 (9), 191 (3), 174 (4), 162 (6), 135 (100).

Tri-tert-butyl 2-[(1E)-N-(tert-butoxycarbonyl)-2-oxo-2-phenylethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate (**12**, $C_{28}H_{24}N_4O_9$)

White solid (49%); m.p.: 172–174 °C; IR (KBr) $\bar{\nu} = 3{,}255$, 2,937, 1,762, 1,745, 1,706, 1,680, 1,596, 1,498, 1,415, 1,369, 1,310, 1,249, 1,105, 1,033, 973 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.37$ (s, 9H), 1.55 (s, 18H), 1.57 (s, 9H), 6.89 (b, 1H), 7.49 (t, $J = 7.6$ Hz, 2H), 7.56 (t, $J = 7.6$ Hz, 1H), 8.18 (d, $J = 7.6$ Hz, 2H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 28.2$, 28.4, 28.5, 82.5, 83.7, 84.8, 128.6, 131.1, 133.5, 135.6, 152.0, 153.8, 157.6, 187.4 ppm; MS (EI, 70 eV): *m/z* (%) = 578 (8), 563 (6), 551 (16), 523 (13), 495 (6), 368 (67), 339 (13), 313 (34), 299 (17), 285 (15), 264 (22), 152 (18), 111 (33), 57 (100).

Tri-tert-butyl 2-[(1E)-N-(tert-butoxycarbonyl)-2-(4-chlorophenyl)-2-oxoethanehydrazonoyl]-hydrazine-1,1,2-tricarboxylate (**13**, $C_{28}H_{41}ClN_4O_9$)

White solid (53%); m.p.: 154–155 °C; IR (KBr) $\bar{\nu} = 3{,}312$, 2,985, 1,770, 1,756, 1,674, 1,583, 1,523, 1,376, 1,329, 1,289, 1,218, 1,015, 771 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.35$ (s, 9H), 1.53 (s, 18H), 1.56 (s, 9H), 7.53 (d, $J = 8.2$ Hz, 2H), 8.46 (d, $J = 8.2$ Hz, 2H), 8.70 (b, 1H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 28.2$, 28.4, 28.5, 82.6, 83.7, 84.8, 129.4, 130.6, 133.9, 135.6, 152.2, 153.6, 157.7, 187.4 ppm.

Triisopropyl 2-[(1E)-2-cyano-N-(isopropoxycarbonyl)-2-oxoethanehydrazonoyl]hydrazine-1,1,2-tricarboxylate (**14**, $C_{18}H_{29}N_5O_8$)

Yellow oil (40%); IR (KBr) $\bar{\nu} = 2{,}984$, 2,357, 1,743, 1,514, 1,463, 1,372, 1,216, 1,085 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.49$ (d, $J = 6.2$ Hz, 6H), 1.54 (d, $J = 6.2$ Hz, 6H), 1.55 (d, $J = 6.2$ Hz, 6H), 1.58 (d, $J = 6.2$ Hz, 6H), 5.28 (m, 4H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 21.8$, 21.9, 22.0, 22.1, 22.2, 71.8, 74.0, 74.9, 75.2, 113.0, 151.1, 151.5, 151.7, 151.9 ppm; MS (EI, 70 eV): *m/z* (%) = 443 (9), 400 (9), 358 (16), 316 (9), 298 (3), 272 (12), 256 (3), 229 (33), 187 (100), 170 (9), 143 (33).

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