Chemical Papers (2023) 77:5091–5095
https://doi.org/10.1007/s11696-023-02846-9

ORIGINAL PAPER

A simple and efficient synthesis of *N*-[3-chloro-4-(4-chlorophenoxy)-phenyl]-2-hydroxy-3,5-diiodobenzamide, rafoxanide

Víctor Kesternich[1] · Marcia Pérez-Fehrmann[1] · Víctor Quezada[1] · Mariña Castroagudín[1] · Ronald Nelson[1] · Rolando Martínez[1]

Received: 19 December 2022 / Accepted: 28 April 2023 / Published online: 12 May 2023

Abstract
A method for the synthesis of rafoxanide **6**, a halogenated salicylanilide used as an efficient anthelmintic in sheep and cattle, is presented. Rafoxanide **6** was synthesized in only three steps from readily available 4-chlorophenol with 74% overall yield. The synthesis has two key stages: the first was salicylic acid iodination, adding iodine in the presence of hydrogen peroxide, which allowed obtaining a 95% yield. The second key stage was the reaction of 3,5-diiodosalicylic acid **5** with aminoether **4**, where salicylic acid chloride was formed in situ with PCl_3 achieving 82% yield. Chemical characterization of both intermediates and final product was achieved through physical and spectroscopic (IR, NMR and MS) techniques.

Keywords Rafoxanide · Salicylanilide · Organoiodine

Introduction

A wide variety of interesting biological properties have been reported for salicylanilides (Waisser et al. 2006; De La Fuente et al. 2006). Furthermore, salicylanilides display potent antifungal and antibacterial activity (Waisser et al. 2001 and 2003; Kuneš et al. 2002; Imramovský et al. 2009; Férriz et al. 2010; Dahlgren et al. 2007; Lal et al. 2021; Miró-Canturri et al. 2020). They have shown activity against gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium,* strains representing a significant problem in clinical practice (Vinsova and Imramovský 2004; Hiramatsu et al. 1997). Otherwise, antimycobacterial activity of salicylanilides has been reported (Waisser et al. 2003; Krátký and Vinšová 2011; Krátký et al. 2012; Le et al. 2022). Additionally, some studies identified the salicylanilide esters of *N*-protected amino acids as selective inhibitors of Interleukin-12p40 production and inhibitors of the protein kinase epidermal growth factor receptor (EGFR PTK) (Kamath and Buolamwini 2006; Liechti et al. 2004; Brown et al. 2008). A recent study showed that some halogenated salicylanilides can reduce SARS-CoV-2 replication and suppress induction of inflammatory cytokines in a rodent model (Blake et al. 2021). Halogenated salicylanilides, are important anthelmintics that are used extensively in the control of Haemonchus spp., Fasciola spp. infestation in sheep and cattle in many countries (Sjogren et al. 1991; Swan 1999), and as potential antileishmanial agents (Lal et al. 2023).

N-[3-Chloro-4-(4-chlorophenoxy)-phenyl]-2-hydroxy-3,5-diiodobenzamide, rafoxanide **6** (Singh et al. 1977; Merck and Co Pat 1968), is a salicylanilide currently used and known for its antihelmintic and fasciolicide properties (Rot et al. 1988; Jabbar et al. 2006; Diiwel and Metzger 1973) and an efficient inhibitor of chitinase in *Onchocerca volvulus* (Gooyit et al. 2014). Recent studies determined that rafoxanide is very effective in treating multiple myeloma (MM) and showed great effectiveness on diffuse large B-cell lymphoma (DLBCL), which is one of the most aggressive lymphoid neoplasms (He, et al. 2020). In addition, rafoxanide promotes apoptosis and autophagy of gastric cancer cells by suppressing PI3K/Akt/mTOR pathway (Liu et al. 2019) and triggers apoptosis and cell cycle arrest in multiple myeloma by enhancing responses to DNA damage, suppressing the p38 MAPK pathway (Xiao et al.2019) and as a novel agent for the treatment of non-small cell lung cancer (Hu et al. 2023) and colorectal cancer (Laudisi et al. 2022).

✉ Víctor Kesternich
vkestern@ucn.cl

[1] Departamento de Química, Facultad de Ciencias, Universidad Católica del Norte, Avda. Angamos 0610, Antofagasta, Chile

Its chemical structure has an amide as its main functional group and three benzene rings with iodine and chlorine atoms, and the last two rings (B and C) linked through a diphenyl ether functional group. In the previous synthesis of rafoxanide described in the bibliography, iodine chloride (ICl) is used as the iodination reagent in the final stage of the synthesis (Merck and Co Pat 1968), a volatile, unstable, toxic and difficult to handle compound, which results in low yields (Zhonghua 2016; Srivastava et al. 1990). On the other hand, it is possible to use preformed 3,5-diiodosalicylic acid (Mrozik et al. 1969). In this sense, obtaining 3,5-diiodosalicylic acid is of great relevance, and several methods have been described: ICl (Woollet et al. 1934), in situ generation of ICl (Imanieh et al. 2011; Kajigaeshi et al. 1987; Palav et al. 2021), *N*-iodosuccinimide (Misal et al. 2021; Wu et al. 2020) or in situ generation of KI_3 (Sharma et al. 2016), in all these cases the yields have been good, but with very little atom economy.

This study describes a synthetic route consisting of only three steps with good overall yield and a more efficient iodination method of salicylic acid.

Experimental

Materials and methods

The reagents and solvents used in this work were obtained from Fluka, Sigma-Aldrich or Merck and used without further purification. Melting points were determined on a Stuart SMP3 and were uncorrected. The infrared spectroscopy (IR) was performed on a Perkin-Elmer FT-IR Spectrometer Spectrum Two with KBr. NMR spectra were recorded in $CDCl_3$, at 500 MHz (Bruker). Chemical shifts were reported in parts per million (δ) using the residual solvent signals ($CDCl_3$: δ_H 7.26, δ_C 77.16) as internal standards for ^1H and ^{13}C NMR spectra and coupling constants (*J*) are reported in Hz. Mass spectra were acquired using IT-MS Bruker AmaZon SL spectrometer. TLC was performed on silica gel Merck 60 F_{254} and TLC plates were visualized by spraying with phosphomolybdic acid reagent and heating.

Preparation of 3-chloro-4-(4′-chlorophenoxy)nitrobenzene 3

A mixture of 4-chlorophenol **2** (12.56 g, 97.7 mmol) and KOH (6.83 g, 121.8 mmol) was heated at 70–80 °C with vigorous stirring until phenol **2** was completely dissolved. Then, fine copper (29 mg, 0.456 mmol) and 3,4-dichloronitrobenzene **1** (11.04 g, 57.5 mmol) were added, and the mixture was stirred at 110–120 °C for 2.5 h. Then it was allowed to reach rt, NaOH 0.8 M (14 mL) was added and the resulting mixture was stirred for 20 min, until a precipitate was formed. The precipitate was filtered and washed with H_2O until neutral pH. Purification of the crude residue by flash chromatography (SiO_2, 10% EtOAc/hexanes) afforded diphenylether **3** as a pale-yellow solid (15.73 g, 96% yield). **m.p.**: 110–112 °C. **IR** cm^{-1}: 3090 (C–H aromatic), 1560–1570 (C=C aromatic). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (d, J = 2.7 Hz, 1H), 8.07 (dd, J = 9.1, 2.7 Hz, 1H), 7.41 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 9.0 Hz, 1H). ^{1}H NMR data according to literature (Fujii et al. 2020). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.65 (C), 153.31 (C), 143.15 (C), 131.09 (C), 130.60 (CH), 126.79 (CH), 125.13 (C), 123.80 (CH), 121.44 (CH), 117.24 (CH). **HRMS-ESI** calculated for $C_{12}H_8Cl_2NO_2$ $[M+H]^+$: 283.9876, found 283.9876.

Preparation of 3-chloro-4-(4′-chlorophenoxy)aminobenzene 4

A mixture of iron powder (0.99 g, 17.74 mmol), diphenylether **3** (1.44 g, 5.07 mmol) and acetic acid (1.13 mL, 19.77 mmol) in EtOH/H_2O (2 mL, 3:1) was refluxed for 2 h. Then, the mixture was cooled to rt and NaOH 1 M was added until pH 7. Solids were removed by filtration and the filtrate was extracted with chloroform. Organic layer was dried over anhydrous sodium sulfate and concentrated to give a crude product that was purified by flash chromatography (SiO_2, 20–50% EtOAc/hexanes) to afford the corresponding aniline **4** as an orange solid (1.21 g, 94% yield). **m.p.:** 74–75 °C. **IR** cm^{-1}: 3400, 3310–3290, 3180 (NH, primary amine), 1460 (C=C aromatic). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (d, J = 6.7 Hz, 2H), 6.89 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 9.0 Hz, 3H), 6.78 (d, J = 2.8 Hz, 1H), 6.57 (dd, J = 8.6, 2.8 Hz, 1H), 3.69 (br s, 2H). ^{1}H NMR data according to literature (Fujii et al. 2020). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.18 (C), 144.49 (C), 143.16 (C), 129.59 (CH), 127.51 (C), 127.21 (C), 123.54 (CH), 117.51 (CH), 116.72 (CH), 114.73 (CH). **HRMS-ESI** calculated for $C_{12}H_{10}Cl_2NO$ $[M+H]^+$: 254.0134, found 254.0135.

Preparation of 3,5-diiodosalicylic acid (5)

Hydrogen peroxide (3.0 mL, 29.37 mmol, 30% in H_2O) was slowly added (20–30 min.) to a mixture of salicylic acid (1.50 g, 10.86 mmol) and iodine (1.50 g, 5.85 mmol) in EtOH (50 mL) at 80 °C. The mixture was refluxed for 2 h and an aqueous solution of $Na_2S_2O_5$ (9.5 mL, 10%) was added at the same temperature. The mixture was then added to H_2O (250 mL) and the precipitate formed was filtered. The product was purified by crystallization in EtOH to afford the 3,5-diiodosalicylic acid **5** as colorless crystals (4.03 g, 95%). **m.p.**: 226–228 °C (according to literature (Imanieh et al. 2011) 233 °C). **IR** cm^{-1}: 3256 (O–H, phenolic), 1667 (C=O), 1582–1480 (C=C, aromatic). **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 11.32 (s, 1H), 8.25 (d, $J = 2.1$ Hz, 1H), 8.17 (d, $J = 2.1$ Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.45 (C), 160.81 (C), 153.15 (CH), 139.32 (CH), 113.17 (C), 87.05 (C), 81.00 (C). **HRMS-ESI** calculated for $C_7H_5I_2O_3$ $[M+H]^+$: 390.8323, found 390.8323.

Preparation of N-[3-chloro-4-(4-chlorophenoxy) phenyl]-2-hydroxy-3,5-diiodobenzamide 6

Phosphorus trichloride (0.11 µL, 1.24 mmol) was added to a mixture of 3-(chloro-4-(4´-chlorophenoxy)aminobenzene **4** (0.316 g, 1.24 mmol) and 3,5-diiodosalicylic acid (0.485 g, 1.24 mmol) in xylene (12 mL) at room temperature. The resulting mixture was warmed up to 110 °C and stirred for 1.5 h. Then, it was allowed to reach room temperature and concentrated. Crude residue was purified by flash chromatography (SiO_2, 10–20% EtOAc/hexanes) to afford the corresponding salicylanilide **6** as a white solid (0.637 g, 82% yield). **m.p.**: 168–170 °C (according to literature (Mrozik et al. 1969) 168–170 °C). **IR** cm^{-1}: 3400 (NH, secondary amide), 1630 (C=O), 1460–1480 (C=C, aromatic). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.47 (s, 1H), 8.20 (d, $J = 1.9$ Hz, 1H), 7.99 (s, 1H), 7.79 (t, $J = 2.3$ Hz, 2H), 7.41 (dd, $J = 8.8$, 2.6 Hz, 1H), 7.30 (d, $J = 8.9$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 1H), 6.90 (d, $J = 8.9$ Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.39 (C), 160.20 (C), 155.59 (C), 151.42 (CH), 149.89 (C), 134.49 (CH), 132.92 (C), 129.99 (CH), 128.77 (C), 126.69 (C), 124.06 (CH), 121.36 (CH), 121.27 (CH), 119.15 (CH), 116.50 (C), 89.12 (C), 80.59 (C). **HRMS-ESI** calculated for $C_{19}H_{12}Cl_2I_2NO_3$ $[M+H]^+$: 625.8278, found 625.8281.

Results and discussion

Scheme 1 shows the route used for synthesizing salicylanilide **6** (Scheme 1). The treatment of 4-chlorophenol **2** with KOH generates the phenoxy ion that reacts, *in situ*, with compound **1** in order to form nitroether **3** (96%). The infrared spectrum of compound **3** shows bands at 3080 from 1560 to 1570 cm^{-1}, typical of C–H and aromatic C=C stretching, respectively. Besides, a band centered at 1420 cm^{-1} corresponding to N–O stretching of the nitro group is shown. In the ^{1}H-NMR spectrum it is possible to observe a doublet ($J = 2.7$ Hz) at 8.38 ppm, corresponding to the proton located in *ortho* respect to the nitro group and the iodine atom, present in ring B. Also, it is possible to see a doublet at 8.07 ppm ($J = 9.0$ Hz), a signal attributable to the second proton *ortho* to the nitro group. At 6.90 ppm appeared a doublet ($J = 9.0$ Hz), corresponding to the *ortho* proton to the oxygen atom of the ether bridge that joins to the two benzene rings, all corresponding to ring B. On the other hand, in the ring C, it is possible to observe an AB system as a doublet at 7.40 ppm ($J = 9.0$ Hz), corresponding to the two *ortho* protons to the ether functional group and, a doublet at 7.03 ppm ($J = 9.0$ Hz) belonging to the two *ortho* protons to the chlorine atom. The ^{13}C NMR spectrum allows us to see the carbon carrying the nitro group at 143.15 ppm and the two carbons linked to the oxygen atom of the ether linkage that joins the two benzene rings, at 158.65 and 153.31 ppm, respectively. The HRMS-ESI analysis showed a molecular ion $[M+H]^+$ of 283.9876, corresponding to the molecular formula $C_{12}H_8Cl_2NO_2$, which corroborated the structure of nitroether **3**. Among the reduction methods for diphenyl ether **3** tested so far (Table 1) (Li et al. 2014; Bellamy and Ou 1984; Lane et al. 2012; Hesse et al. 2013), the reduction with Fe/HOAc provided the aminoether **4** as a crystalline solid in higher yield (94%). The IR spectrum of this compound clearly shows the two primary aromatic amine bands at 3400 and 3310 cm^{-1}. The two protons of the amine functional group appear in the ^{1}H NMR spectrum as a broad

Table 1 Comparative reduction reactions for compound **3**

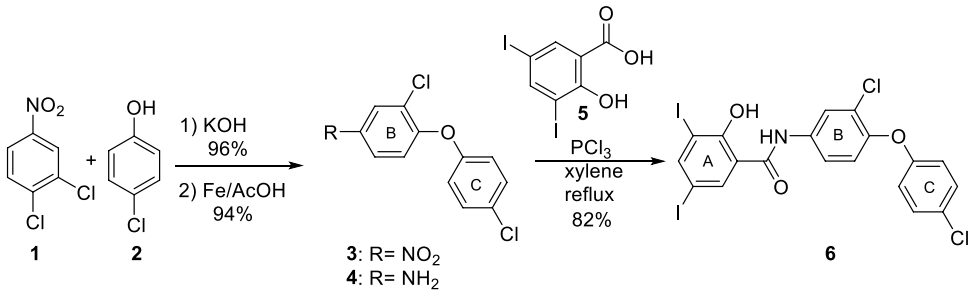
Entry	Method	**3** yield (%)	Refs.
1[a]	Pd–C/NH_2NH_2	Mix. of products	Li et al. (2014)
2	$SnCl_2$/HCl	52%	Bellamy and Ou (1984)
3[b]	Fe/HCl	92%	Lane et al. (2012)
4[c]	Fe/HOAc	94%	Hesse et al. (2013)

[a]Product of dehalogenation was detected

[b]Dark doughy product

[c]Crystalline product

Scheme 1 Synthesis of Rafoxanide



singlet at 3.69 δ. The mass spectrum show a molecular ion $[M+H]^+$ 254.1120 corresponding to $C_{12}H_{10}Cl_2NO$.

On the other hand, the synthesis of 3,5-diiodosalicylic acid (**5**) was carried out from salicylic acid using 0.5 equivalents of I_2 in the presence of hydrogen peroxide as oxidizing agent. This methodology allowed obtaining compound **5** with 95% yield in an efficient process and with great atom economy. The IR spectrum of 3,5-diiodosalicylic acid (**5**) shows intense bands at 3256, 1667 and 1582 cm^{-1}, typical of O–H, C=O and C=C stretching, respectively. In the ^{1}H-NMR spectrum it is possible to observe a singlet at 11.32 ppm, corresponding to phenolic proton, and two doublets at 8.25 and 8.17 ppm ($J = 2.14$ Hz), corresponding to the aromatic protons of 3,5-diiodosalicylic acid. In the ^{13}C-NMR spectrum the carboxylic C=O is observed at 170.45 ppm, the four quaternary carbons of the benzene ring at 160.81, 113.17, 87.05 and 81.00 ppm, and the two CH at 153.15 and 139.32 ppm. HRMS-ESI analysis showed a molecular ion $[M+H]^+$ of 390.8323, corresponding to the molecular formula $C_7H_5I_2O_3$, which corroborated the structure of compound **5**.

Finally, the condensation between **4** and 3,5-diiodosalicylic acid **5** was the key step of the synthesis since it was done in a one-pot procedure by forming, in situ, the corresponding acid chloride with PCl_3, thus giving rafoxanide **6** in 82% yield using xylene as solvent, compared to 52% yield using toluene. Unlike the methods previously described (Kahl et al. 2011), the intermediate chloride formed does not need to be isolated and purified before carrying out the condensation reaction leading to the amide. The IR spectrum showed the characteristic band of the N–H bond of the amide at 3400 cm^{-1} and the carbonyl band at 1630 cm^{-1} In the ^{1}H NMR spectrum it is possible to see all protons located in ring A. At 8.20 ppm a doublet ($J = 1.9$ Hz) corresponding to the *ortho* proton to the carbonyl group of the amide and at 7.99 ppm a singlet corresponding to the *ortho* proton to the two iodine atoms. These results are consistent with the mass spectrum that shows a molecular ion $[M+H]^+$ 625.8278 corresponding to $C_{19}H_{12}Cl_2I_2NO_3$, and would be indicative of the presence of the tetra substituted ring derived from 3,5-diiodosalicylic acid, in the structure of rafoxanide **6**.

The method we described herein represents an advantageous alternative procedure for the preparation of new salicylanilides with structures related to rafoxanide.

Conclusion

The present research allowed us to synthesize the halogenated salicylanilide, rafoxanide, in only three steps, with an overall yield of 74%, from simple, cheap and efficient reagents. In addition, a new method of iodination of salicylic acid based on the use of I_2 and hydrogen peroxide with high yield and great atom economy is proposed. Therefore, this method represents a novel and cost-effective alternative process for obtaining rafoxanide and its derivatives.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11696-023-02846-9.

Acknowledgements This study was financed by Dirección General de Investigación y Postgrados (DGIP) Universidad Católica del Norte, Antofagasta, Chile.

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