ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 5, pp. 730–733. © Pleiades Publishing, Ltd., 2019.
Russian Text © The Author(s), 2019, published in Zhurnal Organicheskoi Khimii, 2019, Vol. 55, No. 5, pp. 805–809.

SHORT COMMUNICATIONS

Synthesis of Dialkyl 5-Amino-2-hydroxy-4,6-dimethylisophthalates and Their Sulfonylation

I. G. Povarov[a,*], N. A. Shilenkov[a], I. V. Peterson[b], G. A. Suboch[a], and M. S. Tovbis[a]

[a] *Reshetnev Siberian State University of Science and Technology, pr. imeni gazety "Krasnoyarskij rabochii" 31, Krasnoyarsk, 660037 Russia,*

[b] *Institute of Chemistry and Chemical Technology, Siberian Branch, Russian Academy of Sciences, Akademgorodok 50/24, Krasnoyarsk, 660036 Russia*

**e-mail: povarov_i@mail.ru*

Received November 10, 2018; revised February 10, 2019; accepted February 17, 2019

Abstract—Dimethyl 5-amino-2-hydroxy-4,6-dimethylisophthalate and dimethyl 5-amino-2-hydroxy-4,6-dimethylisophthalate were obtained in the free form for the first time. The products were sulfonylated with *p*-toluenesulfonyl to obtain previously unknown dialkyl 5-(4-toluenesulfonamido)-2-hydroxy-4,6-dimethylisophthalates. The use of *p*-acetamidobenzenesulfonyl chloride as the sulfonylating agent in this reaction led to the formation of dialkyl 5-(4-acetamidobenzenesulfonamido)-2-hydroxy-4,6-dimethyl isophthalates. The synthesized sulfonamide derivatives are of interest as potentially biologically active compounds. The structure of all the obtained compounds was proved using IR and NMR spectroscopy and mass spectrometry.

Keywords: synthesis, sulfonylation, *p*-toluenesulfonyl chloride, *p*-acetamidobenzenesulfonyl chloride, aminoisophthalates, IR spectroscopy, NMR spectroscopy, mass spectrometry

DOI: 10.1134/S1070428019050269

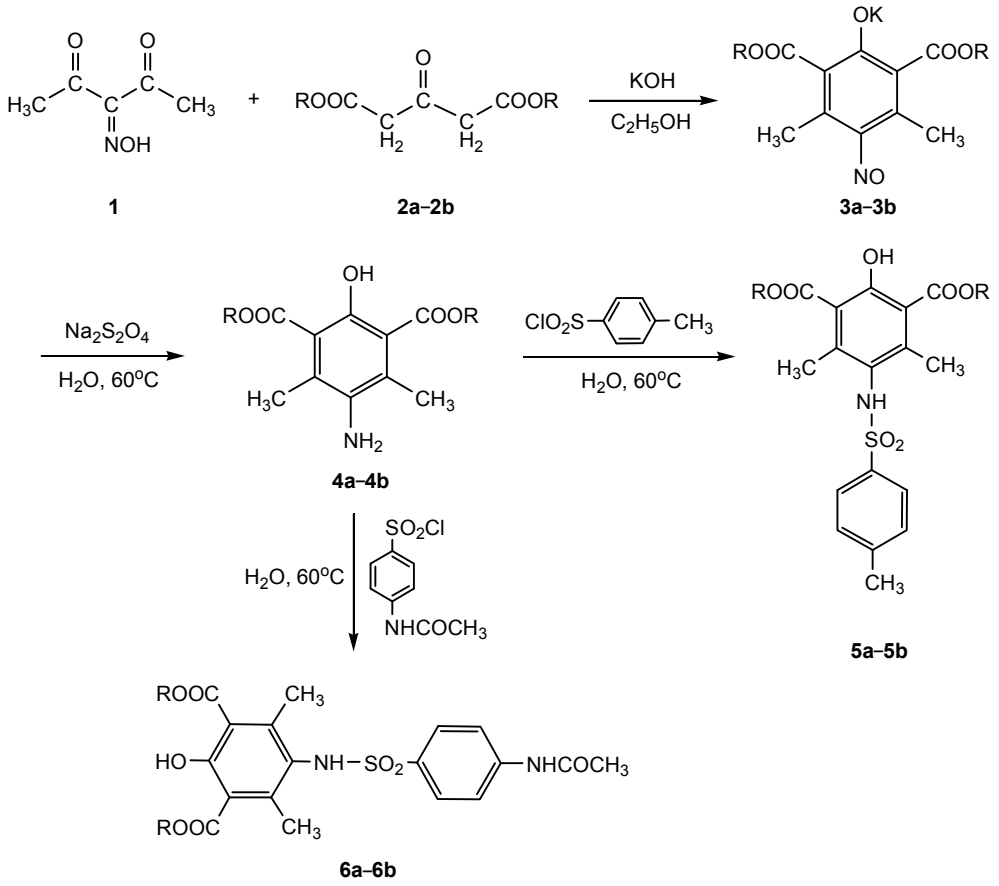
At present a lot of different derivatives of aminophenols have been synthesized. Of great practical importance are *para*-aminophenols and *para*-acetamidophenols, because their derivatives are used in medicine as analgesics, antipyretics, and other drugs [1]. Some persubstituted aminophenols containing ester groups in the benzene ring exhibit analgesic, anti-inflammatory, and antiarrhythmic activity [2, 3].

Often aromatic amines are used in medicine not in the free form but as sulfonated derivatives. Thus, the known sulfonamide derivatives, broad-spectrum antibacterial drugs active against both gram-positive and gram-negative microorganisms, were introduced into medical practice even before the discovery of penicillins [4]. We previously synthesized a series of hydrochlorides of persubstituted aminophenols [5]. At the same time, free aminophenol have never been prepared and studied.

The present communication reports the first synthesis of persubstituted aminophenols both in the free form and as sulfonated derivatives, which hold promise as potentially biologically active compounds. To this end, we first prepared nitrosophenols containing ester groups in the 2 and 6 positions with respect to hydroxyl [6]. The products were reduced and treated with *p*-toluenesulfonyl chloride or *p*-acetamidobenzenesulfonyl chloride to isolate previously unknown sulfonated derivative of persubstituted aminophenols, whose structure was proved by means of IR and ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

Dialkyl 2-hydroxy-4,6-dimethyl-5-(*p*-toluenesulfonamido)isophthalates **5a**, **5b** and 5-(*p*-acetamidobenzenesulfonamido)-2-hydroxy-4,6-dimethylisophthalates **6a**, **6b** (see scheme) were prepared by the cycloaromatization of isonitrosoacetylacetone **1** and dimethyl or diethyl acetonedicarboxylate **2a** and **2b**. as a result, we obtained known persubstituted nitrosophenols as potassium salts **3a** and **3b**. These salts were reduced with sodium dithionite by the procedure in [7] to form corresponding aminophenols **4a** and **4b**. The subsequent sulfonylation of the latter compound with

Scheme 1.



p-toluenesulfonyl chloride or *p*-acetamidobenzenesulfonyl chloride gave sulfonated derivatives **5a**, **5b** or **6a**, **6b**.

Diethyl 5-amino-2-hydroxy-4,6-dimethylisophthalate (4a). Potassium 2,6-bis(ethoxycarbonyl)-3,5-dimethyl-4-nitrosophenoxide, 0.5 g (1.69 mmol), was dissolved in 10 mL of water at 60°C, after which 0.5 g (2.87 mmol) of sodium dithionite was added in small portions, and the mixture was stirred for 60 min. The reaction progress was monitored by TLC (toluene–ethyl acetate, 1 : 1). The mixture was then cooled to room temperature, and the precipitate that formed was filtered off and dried over $CaCl_2$. Yield 0.2 g (40%). Yellow crystals, mp 72–75°C. IR spectrum, ν, cm^{-1}: 1731 (C=O), 3373–3450 (NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.82 s (1H, OH), 4.42 s (2H, NH_2), 4.25–4.42 q (4H, $COCH_2$), 1.27–1.29 q (6H, ester CH_3). ^{13}C NMR spectrum, δ, ppm: 14.3, 15.4, 61.1, 121.4, 121.6, 138.2, 143.0, 168.4. Mass spectrum, *m/z* (I_{rel}, %): 281 (34) $[M]^+$, 235 (90), 189 (65), 106 (45), 77 (28), 29 (94). UV spectrum (ethanol): λ_{max} 216 nm, ε 332; λ_{max} 388 nm, ε 86.

Dimethyl 5-amino-2-hydroxy-4,6-dimethylisophthalate (4b). Potassium 2,6-bis(methoxycarbonyl)-3,5-dimethyl-4-nitrosophenoxide, 0.5 g (1.87 mmol), was dissolved in 10 mL of water at 60°C, after which 0.5 g (2.87 mmol) of sodium dithionite was added in small portions, and the mixture was stirred for 30 min. The mixture was then cooled to room temperature, and the precipitate that formed was filtered off and dried over $CaCl_2$. Yield 0.22 g (42%). Yellow crystals, mp 77–79°C. IR spectrum, ν, cm^{-1}: 1754 (C=O), 3373-3455 (NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.85 s (1H, OH), 4.53 s (2H, NH_2), 4.15–4.39 s (4H, $COCH_3$), 1.19–1.33 q (6H, ester CH_3). ^{13}C NMR spectrum, δ, ppm: 15.5, 52.3, 121.4, 121.5, 138.2, 142.8, 168.8. Mass spectrum, *m/z* (I_{rel}, %): 253 (24) $[M]^+$ 221 (93), 189 (56), 106 (34), 77 (18), 15 (25).

Diethyl 2-hydroxy-4,6-dimethyl-5-(4-methylbenzenesulfonamido)isophthalate (5a). Compound **4a**, 0.1 g (0.36 mmol), was dissolved in 4 mL of water, after which 0.075 g (0.39 mmol) of *p*-toluenesulfonyl chloride and 0.03 g (0.28 mmol) of Na_2CO_3 were added in small portions over a period of 1 h under

stirring and heating at 60°C, ensuring that the reaction of the medium was neutral. The mixture was then stirred for 2 h at 60°C, controlling the reaction progress by TLC (toluene–ethyl acetate, 1 : 1), and cooled to room temperature. To remove unreacted aminophenol, the mixture was made acidic with HCl (by Congo test) and stirred for 30 min. The precipitate that formed was filtered off, washed with water until neutral washings, and recrystallized from aqueous alcohol. The precipitate was dried under vacuum. Yield 0.066 g (66%), light beige crystals. mp 143–145°C. IR spectrum, ν, cm^{-1}: 3232 (NH), 1380 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.93 s (1H, OH), 10.13 s (1H, NH) 4.24–4.28 q (4H, $COCH_2$), 1.24–1.26 t (3H, ester CH_3). ^{13}C NMR spectrum, δ, ppm: 14.2, 16.5, 21.3, 61.4, 121.5, 126.2, 126.8, 130.0, 138.8, 139.0, 143.3, 151.4, 167.27. Mass spectrum, *m/z* (I_{rel}, %): 435 (50) $[M]^+$, 390 (25), 280 (64), 234 (88), 206 (33), 91 (40), 29 (31). UV spectrum (ethanol): λ_{max} 218 nm, ε 628; λ_{max} 317 nm, ε 96.

Dimethyl 2-hydroxy-4,6-dimethyl-5-(4-methylbenzenesulfonamido)isophthalate (5b). Compound **4b**, 0.1 g (0.39 mmol), was dissolved in 4 mL of water, after which 0.075 g (0.39 mmol) of *p*-toluenesulfonyl chloride and 0.03 g (0.28 mmol) of Na_2CO_3 were alternately added in small portions over a period of 1 h under stirring and heating at 60°C. Reaction control and further workup was similar to those described for compound **5a**. Yield 0.075 g (75%), light beige crystals. mp 202–205°C. IR spectrum, ν, cm^{-1}: 3225 (NH), 1378 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.37 s (1H, OH), 10.12 s (1H, NH), 3.78 s (6H, $COCH_3$), 7.38–7.56 d (4H, tosyl ring), 2.39 s (3H, tosyl CH_3), 1.87 s (6H, aminophenol CH_3). ^{13}C NMR spectrum, δ, ppm: 16.6, 21.3, 52.6, 121.4, 126.3, 126.7, 130.0, 139.0, 139.1, 143.3, 151.2, 167.7. Mass spectrum, *m/z* (I_{rel}, %): 407 (74) $[M]^+$, 376 (21), 252 (76), 220 (96), 192 (29), 91 (49), 65 (15).

Diethyl 5-(4-acetamidobenzenesulfonamido)-2-hydroxy-4,6-dimethylisophthalate (6a). Compound **4a**, 0.2 g (0.71 mmol), was dissolved in 4 mL of water, after which 0.2 g (0.86 mmol) of *p*-acetamidobenzenesulfonyl chloride and 0.059 g (0.56 mmol) of Na_2CO_3 were alternately added in small portions over a period of 1.5 h under stirring and heating at 60°C. Reaction control and further workup was similar to those described for compound **5a**. Yield 80%, mp 150–152°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 10.38 (1H, NH); 9.93 s (1H, OH); 9.31 s (1H, tosyl NH); 7.56–7.76 d (4H, tosyl ring); 4.24–4.28 q (4H, ester CH_2), 1.24–1.26 t (6H, ester CH_3); 1.88 s (6H, aminophenol CH_3); 2.09 s (3H, tosyl CH_3). ^{13}C NMR spectrum, δ, ppm: 14.2, 16.5, 24.4, 61.4, 118.1, 118.9, 121.5, 126.4, 127.9, 135.2, 139.0, 143.4, 151.4, 167.3, 169.3. Mass spectrum, *m/z* (I_{rel}, %): 475 (73) $[M]^+$, 458 (15), 413 (6.91), 401 (2.52), 359 (34), 357 (59), 355 (29), 264 (20), 228 (36).

Dimethyl 5-(4-acetamidobenzenesulfonamido)-2-hydroxy-4,6-dimethylisophthalate (6b). *p*-Acetamidobenzenesulfonyl chloride, 0.2 g (0.86 mmol), and 0.059 g (0.56 mmol) of Na_2CO_3 were alternately added in small portions over a period of 1 h to a stirred and heated (30°C) solution of 0.2 g (0.79 mmol) of compound **4b** in 4 mL of water. Reaction control and further workup was similar to those described for compound **5a**. Yield 75%, mp 200–202°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm:10.52 (1H, NH); 10.00 s (1H, OH); 9.72 s (1H, tosyl NH); 7.70–7.85 d (4H, tosyl ring); 3.89 s (6H, $COCH_3$); 2.23 s (6H, aminophenol CH_3); 2.03 s (3H, tosyl CH_3). ^{13}C NMR spectrum, δ, ppm: 16.1, 22.3, 51.4, 118.2, 118.8, 121.3, 125.3, 126.9, 134.3, 138.0, 143.0, 152.3, 166.8, 168.8. Mass spectrum, *m/z* (I_{rel}, %): 450 (74) $[M]^+$, 372 (15), 331 (41), 317 (100), 295 (22), 236 (3), 194 (10), 135 (2), 115 (5).

The IR spectra were obtained on a Bruker Tensor-27 FTIR spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance III 600 spectrometer at 600.13 (^1H) and 150.9 (^{13}C) MHz.

The mass spectra were obtained on a Shimadzu LC/MS-2020 instrument, column RAPTORARC-18 100, isocratic mode, flow rate 20 μL/min, column temperature 35°C, sample concentration 0.01 mg/mL; an ESI source was operated.

ACKNOWLEDGEMENTS

The work performed using the equipment of the Center for Colletive Use, Krasnoyarsk Research Center, Siberian Branch, Russian Academy of Sciences.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Iqbal, Z., *Pakistan J. Sci*., 2003, vol. 55, p. 29.
2. Eiden, F., Leister, H.P., and Mayer, D., *Arzneimittel-Forschung*, 1983, vol. 33, p. 101.

3. Komar, N.A., Slashchinin, D.G., Suboch, G.A., and Tovbis, M.S., *Pharm. Chem. J*., 2014, vol. 48, p. 534. doi 10.1007/s11094-014-1145-0
4. Krasnyuk, I.I. and Mikhailova, G.V., *Praktikum po tekhnologii lekarstvennykh form* (Workshop on technology dosage forms), Moscow: Izd. "Akademiya", 2006.
5. Slashchinin, D.G., Tovbis, M.S. Root, E.V., Zadov, V.E., and Sokolenko, W.A., *Russ. J. Org. Chem*., 2010, vol. 46, p. 517. doi 10.1134/S1070428010040111
6. Konovalov, A.I., Antipin, I.S., Burilov, V.A., Madzhidov, T.I., Kurbangalieva, A.R., Nemtarev, A.V., Solovieva, S.E., Stoikov, I.I., Mamedov, V.A., Zakharova, L.Ya., Gavrilova, E.L., Sinyashin, O.G., Balova, I.A., Vasil'ev, A.V., Zenkevich, I.G., Krasavin, M.Yu., Kuznetsov, M.A., Molchanov, A.P., Novikov, M.S., Nikolaev, V.A., Rodina, L.L., Khlebnikov, A.F., Beletskaya, I.P., Vatsadze, S.Z., Gromov, S.P., Zyk, N.V., Lebedev, A.T., Lemenovskii, D.A., Petrosyan, V.S., Nenaidenko, V.G., Negrebetskii, V.V., Baukov, Yu.I., Shmigol', T.A., Korlyukov, A.A., Tikhomirov, A.S., Shchekotikhin, A.E., Traven', V.F., Voskresenskii, L.G., Zubkov, F.I., Golubchikov, O.A., Semeikin, A.S., Berezin, D.B., Stuzhin, P.A., Filimonov, V.D., Krasnokutskaya, E.A., Fedorov, A.Yu., Nyuchev, A.V., Orlov, V.Yu., Begunov, R.S., Rusakov, A.I., Kolobov, A.V., Kofanov, E.R., Fedotova, O.V., Egorova, A.Yu., Charushin, V.N., Chupakhin, O.N., Klimochkin, Yu.N., Osyanin, V.A., Reznikov, A.N., Fisyuk, A.S., Sagitullina, G.P., Aksenov, A.V., Aksenov, N.A., Grachev, M.K., Maslennikova, V.I., Koroteev, M.P., Brel', A.K., Lisina, S.V., Medvedeva, S.M., Shikhaliev, Kh.S., Suboch, G.A., Tovbis, M.S., Mironovich, L.M., Ivanov, S.M., Kurbatov, S.V., Kletskii, M.E., Burov, O.N., Kobrakov, K.I., and Kuznetsov, D.N., *Russ. J. Org. Chem*., 2018, vol. 54, p. 157. doi 10.1134/S107042801802001X
7. Persidskaya, D.I., Povarov, I.G., Efimov, V.V., Lyubyashkina, A.V., Suboch, G.A., and Tovbis, M.S., *Zh. Sib. Fed. Univer., Ser. Khim*., 2018, vol. 11, p. 369. doi 10.17516/1998-2836-0083