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N-Alkylation and N-Acylation of 2,4-Dinitrophenylamine by Ultrasound Irradiation

ALI KHALAJ*, ALIREZA DOROUDI†, NEDA ADIBPOUR† and GILA MOHSENI ARAGHI
Department of Medicinal Chemistry, Faculty of Pharmacy
Tehran Medical Sciences University, Tehran, Iran
Fax: (98)(21)66461178; P.O. Box 14155/6451; E-mail: khalaj@ams.ac.ir

By ultrasound irradiation, the weakly nucleophilic amine of 2,4-dinitrophenylamine was alkylated and acylated in acetonitrile in presence of sodium hydride in high yields at short period of the reaction times.

Key Words: Ultrasound, N-Alkylation, 2,4-Dinitrophenylamine, N-Acylation.

INTRODUCTION

During the course of investigation on the synthesis of some radiosensitizers is required to prepare N-alkyl and N-bromoalkyl-2,4-dinitrophenylamine (**4a-f**) and N-(2,4-dinitrophenyl)alkanamides (**5a-e**) as intermediates. Due to the low nucleophilicity of the amine group of 2,4-dinitrophenylamine (**1**), N-alkylation and N-acylation of this compound by the conventional methods through the reaction with alkyl and acyl halides are difficult and only one example for the formation of N-propyl-2,4-dinitrophenylamine (**4a**)[1] and one patent[2] for the preparation N-(2,4-dinitrophenyl)alkanamides (**5**) (n = 6-16) by the classical methods have been described in the literature. The most common method for the preparation of N-alkyl-2,4-dinitrophenylamines (**4**) are the reaction of alkyl amines with 2,4-dinitrohalobenzens[3,4] which are more expensive than 2,4-dinitrophenylamine (**1**) and the method has been used for analyses of amines by chromatographic methods. Also an effective method for the preparation of N-(2,4-dinitrophenyl)alkanamides (**5**) has been subjected to acylation of 2,4-dinitro-phenylamine (**1**) with silylcarboxylates *via* mixed anhydrides in the presence of a catalyst[5,6]. The main drawbacks of this approach are expensive reagents, difficulties in preparation of the starting substrates and long reaction time (20 h). In the search for an effective and convenient method for the synthesis of **4a-f** and **5a-e**, the application of ultrasound shown to increase the rate and yields of a large number of organic transformations[7] for alkylation and acylation of the weakly nucleophilic amine of 2,4-dinitrophenylamine **1**.

†Department of Medicinal Chemistry, Faculty of Pharmacy, Ahvaz Jundishapour Medical Sciences University, Ahvaz, Iran.

EXPERIMENTAL

All the chemical and solvents were from Merck (Germany) and used without further purifications. Melting points were determined on a Reichert hot plate and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (400 MHz) using $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Mass spectra were obtained on a Finningan TSQ-70 instrument. Infrared spectra were recorded on a Nicolet Magna IR 550 spectrometer. Elemental analyses for C, H and N were performed using a Heracus CHN-O-rapid elemental analyzer and the results are within ± 0.4 % of the theoretical values. Sonication was performed in a Liarre Ultrasonic 35 (Italy) with a frequency of 28-34 KHz at a nominal power of 80-180 W.

General procedure for the synthesis of N-alkyl and N-acyl, 2,4-nitrophenylamine (4) and N-(2,4-dinitrophenyl)alkanamides (5): To a stirred solution of 2,4-dinitro phenylamine (**1**) (183 mg, 1 mmol) in acetonitrile (10 mL) in 50 mL Pyrex flask was added sodium hydride (24 mg, 1 mmol). After 10 min, the stirred mixture was treated with corresponding alkyl bromides **2** or acyl chlorides **3** (2 mmol) and the reaction mixture while monitored by TLC were sonicated at 40 °C in a thermostatic bath for 45 min. The solvent was then evaporated under reduced pressure and water (10 mL) was added to the residue, the pH of the resulting mixture was brought to 2 by addition of HCl and then was extracted with hexane (3 × 10 mL). The organic layers were combined, washed with brine (2.5 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed in vacuum. For the preparation of N-(2,4-dinitrophenyl)-alkanamides **5**, residues were subjected to flash chromatography (chloroform) and residues after evaporation of chloroform were crystallized from ethyl acetate-heptane For the purification of N-alkyl-2,4-dinitro phenylamine (**4**), residues were crystallized from ethyl acetate-heptane.

N-(1-Propyl)-2,4-dinitrophenylamine[3] (4a): Yield 53.3 %; m.p. 88-89 °C (90-91 °C); ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 0.98 (3H, t, J = 7.2 Hz, CH_3), 1.70-1.85 (2H, m, CH_2), 3.40-3.48 (2H, m, NCH_2), 6.84 (1H, d, J = 9.6 Hz, 6-ArH), 8.26 (1H, dd, $J_{3,5}$ = 2.4 Hz, $J_{5,6}$ = 9.6 Hz, 5-ArH), 8.58 (1H, br, s, NH), 9.16 (1H, d, J = 2.4Hz, 3-ArH); IR (KBr, ν_{max}, cm^{-1}): 3370 (NH), 1622 & 1519 (phenyl), 1338 (CH_3); MS (m/z %): 225 (64), 196 (100), 150 (10); Anal. calcd. for $C_9H_{11}N_3O_4$ (m.w. 225.07): C 48.00, H 4.92, N 18.66. Found: C 47.94, H 4.93, N 18.67.

N-(1-Buthyl)-2,4-dinitrophenylamine (4b): Yield 58.5 %; m.p. 85-87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J = 7.2 Hz, CH_3), 1.45-1.55 (2H, m, CH_2), 1.70-1.80 (2H, m, CH_2), 3.35-3.55 (2H, m, NCH_2), 6.84 (1H, d, J = 9.6 Hz, 6-ArH), 8.26 (1H, dd, $J_{3,5}$ = 2.4, $J_{5,6}$ = 9.6 Hz, 5-ArH), 8.58 (1H, br,s, NH), 9.16 (1H, d, J = 2.4 Hz, 3-ArH); IR (KBr, ν_{max}, cm^{-1}): 3360 (NH), 1618 & 1510 (phenyl), 1384 (CH_3); Ms (m/z %): 239 (78), 196 (100), 180 (18.5); Anal. calcd. for $C_{10}H_{13}N_3O_4$ (239.09): C 50.21, H 5.48, N 17.56. Found: C 50.32, H 5.49, N 17.50.

N-(1-Pentyl)-2,4-dinitrophenylamine (4c): Yield 59.2 %; m.p. 54-55 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 (3H, t, *J* = 7.2 Hz, CH_3), 1.35-1.44 (2H, m, CH_2), 1.55-1.65 (2H, m, CH_2), 1.80-1.90 (2H, m, CH_2), 3.45-3.55 (2H, q, NCH_2), 6.92 (1H, d, *J* = 9.6 Hz, 6-ArH), 8.26 (1H, dd, $J_{3,5}$ = 2.4, $J_{5,6}$ = 9.6 Hz, 5-ArH), 8.58 (1H, br, s, NH), 9.18 (1H, d, *J* = 2.4 Hz, 3-ArH); IR (KBr, ν_{max}, cm^{-1}): 3414 (NH), 1622 & 1519 (phenyl), 1335 (CH_3); Ms (m/z %): 253 (25), 196 (100); Anal. calcd. for $C_{11}H_{15}N_3O_4$ (m.w. 253.11): C 52.16, H 5.96, N 16.59. Found: C 52.28, H 5.85, N 16.46.

N-(3-Bromopropyl)-2,4-dinitrophenylamine (4d): Yield 72 %; m.p. 72-73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.20-2.35 (2H, m, CH_2), 3.54 (2H, t, *J* = 6.8 Hz, NCH_2), 3.6-3.7 (2H, m, CH_2 Br), 6.92 (1H, d, *J* = 9.6 Hz, 6-ArH), 8.26(1H, dd, $J_{3,5}$ = 2.4 Hz, $J_{5,6}$ = 6.8 Hz, 5-ArH), 8.62 (1H, br, s, NH), 9.16 (1H, d, 2.8 Hz, 3-ArH); IR (KBr, ν_{max}, cm-1): 3365 (NH), 1613 & 1511 (phenyl); MS (m/z %): 302, 304 (40), 223 (45), 195 (100), 129 (35), 102 (20); Anal. calcd. for $C_9H_{10}N_3O_4Br$ (m.w. 302.99): C 35.54, H 3.31, N 13.82. Found: C 35.57, H 3.33, N 13.47.

N-(4-Bromobutyl)-2,4-dinitrophenylamine (4e): Yield 57 %; m.p. 71-72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.88-2.12 (4H, m, 2 × CH_2), 3.40-3.70 (4H, m, NCH_2 & CH_2Br), 6.92 (1H, d, *J* = 9.6 Hz, 6-ArH), 8.18 (1H, dd, $J_{3,5}$ = 2.4 Hz, $J_{5,6}$ = 9.6 Hz, 5-ArH), 8.64 (1H, d, *J* = 2.4 Hz, NH), 9.12 (1H, d, *J* = 2.4 Hz, 3-ArH); IR (KBr, ν_{max}, cm^{-1}): 3335 (NH), 1618 & 1501 (phenyl); MS (m/z %): 317, 319 (12), 237 (95), 220 (100), 189 (100), 180 (20); Anal. calcd. for $C_{10}H_{12}N_3O_4Br$ (m.w. 317.00): C 37.75, H 3.80, N 13.21. Found: C 37.35, H 3.95, N 13.23.

N-(5-bromopentyl)-2,4-dinitro-phenylamine (4f): Yield 66%; m.p. 71-73°C; 1H NMR (CDCl3, 400 MHz): d 1.60-1.70 (2H, m, CH2), 1.75-1.88(2H, m, CH2), 1.90-199(2H, m, CH2), 1.9-1.99, 3.34-3.40 (4H, m, NCH2 &CH2Br), 6.88 (1H, d, *J* = 9.6Hz, 6-ArH), 8.30 (1H, dd, $J_{3,5}$ = 2.8, $J_{5,6}$ = 9.6 Hz, 5-ArH), 8.56 (1H, br, s, NH), 9.20 (1H, d, *J* =2.8 Hz, 3-ArH); IR (KBr, ν_{max}, cm^{-1}): 3344 (NH), 1623 and 1521 (phenyl); MS (m/z %): 331,333(15), 252(100), 196(85); Anal. calcd. for $C_{11}H_{14}N_3O_4Br$ (m.w. 331.02): C 39.78, H 4.25, N 12.65. Found: C 39.59, H 4.19, N 12.46.

N-(2,4-Dinitrophenyl)hexanamide (5a): Yield 78.3 %; m.p. 79-81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (3H, t, *J* = 7.2 Hz, CH_3), 1.35-1.42 (4H, m, 2 × CH_2), 1.70-1.83 (2H, m, CH_2), 2.56 (2H, t, *J* = 7.6 Hz, CH_2CO), 8.44 (1H, dd, $J_{3,5}$ = 2.4Hz, $J_{5,6}$ = 9.6 Hz, 5-ArH), 9.13 (1H, d, *J* = 9.6 Hz, 6-ArH), 9.15 (1H, d, *J* = 2.4 Hz, 3-ArH), 10.52 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3329 (NH), 1710 (CO), 1501 (phenyl), 1352 (CH_3); MS (m/z %): 281 (40), 225 (80), 196 (45), 183 (30), 99 (25), 71 (55), 55 (30), 43 (100); Anal. calcd. for $C_{12}H_{15}N_3O_5$ (m.w. 281.10): C 51.24, H 5.37, N 14.93. Found: C 50.93, H 5.19, N 15.25.

N-(2,4-Dinitrophenyl)heptanamide (5b): Yield 91 %; m.p. 57-59 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (3H, t, *J* = 7.2 Hz, CH_3), 1.25-1.45 (4H, m, 2 × CH_2), 1.55-1.68 (2H, m, CH_2), 1.70-1.83 (2H, m, CH_2), 2.56 (2H, t, *J* = 8 Hz, CH_2CO), 8.48 (1H, dd, $J_{3,5}$ = 2.4 Hz, $J_{5,6}$ = 9.6 Hz, 5-ArH), 9.13 (1H, d, *J* = 9.6 Hz, 6-ArH), 9.15 (1H, d, *J* = 2.4 Hz, 3-ArH), 10.70 (1H, s, NH); IR (KBr, ν_{max}, cm^{-1}): 3339

(NH), 1721 (CO), 1511 (phenyl), 1347 (CH_3); MS (m/z %): 295 (35), 225 (75), 196 (30), 183 (44), 113 (100), 85 (25), 57 (20), 43 (43); Anal. calcd. for $C_{13}H_{17}N_3O_5$ (m.w. 295.12): C 52.87, H 5.80, N 14.23. Found: C 52.66, H 5.87, N 14.31.

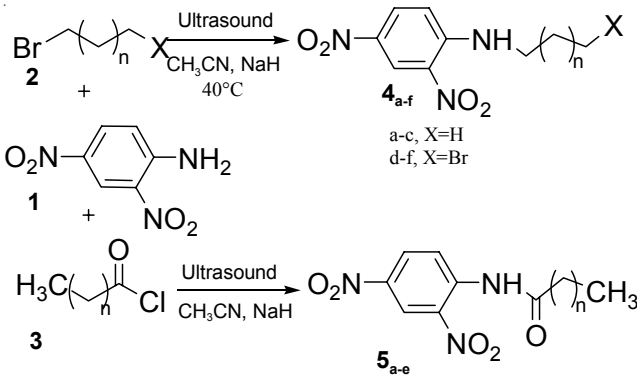
N-(2,4-Dinitrophenyl)octanamide[2] (5c): Yield 59 %; m.p. 61-62 °C (64-65 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (3H, t, J = 7.2 Hz, CH_3), 1.22-1.44 (8H, m, 4 × CH_2), 1.72-1.81 (2H, m, CH_2), 2.56 (2H, t, J = 7.6, CH_2CO), 8.48 (1H, dd, $J_{3,5}$ = 2.8 Hz, $J_{5,6}$ = 9.6 Hz, 5-ArH), 9.13 (1H, d, J = 9.6 Hz, 6-ArH), 9.15 (1H, d, J = 2.8Hz, 3-ArH), 10.64 (1H, s, NH); IR (KBr, ν_{max}, cm^{-1}): 3334 (NH), 2924, 2847 (CH_2), 1705 (CO), 1506 (phenyl), 1357 (CH_3); MS (m/z %): 309 (30), 225 (44), 196 (24), 183 (20), 127 (58); Anal. calcd. for $C_{14}H_{19}N_3O_5$ (m.w. 309.13): C 54.36, H 6.19, N 13.58. Found: C 54.31, H 6.18, N 13.56.

N-(2,4-Dinitrophenyl)nonanamide (5d): Yield 82.5 %; m.p. 63-69 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (3H, t, J = 7.2 Hz, CH_3), 1.20-1.44 (10H, m, 5 × CH_2), 1.72-1.82 (2H, m, CH_2), 2.56 (2H, t, J = 7.6 Hz, CH_2CO), 8.48 (1H, dd, $J_{3,5}$ = 2.8 Hz, $J_{5,6}$ = 9.6 Hz, 5-ArH), 9.13 (1H, d, J = 9.2 Hz, 6-ArH), 9.16 (1H, d, J = 2.8 Hz, 3-ArH), 10.66 (1H, s, NH); IR (KBr, ν_{max}, cm^{-1}): 3344 (NH), 2919, 2842 (CH_2), 1710 (CO), 1506 (phenyl), 1362 (CH_3); MS (m/z %): 323 (25), 267 (10), 225 (65), 196 (40), 141 (100), 71 (45), 57 (79), 43 (36); Anal. calcd. for $C_{15}H_{21}N_3O_5$ (m.w. 323.15): C 55.71, H 6.54, N 12.99. Found: C 55.63, H 6.36, N 12.89.

N-(2,4-Dinitrophenyl)decanamide (5e): Yield 84 %; m.p. 61-62 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (3H, t, J = 7.2 Hz, CH_3), 1.20-1.45 (12H, m, 6 × CH_2), 1.7-1.8 (2H, m, CH_2), 2.56 (2H, t, J = 7.7 Hz, CH_2CO), 8.47 (1H, dd, $J_{3,5}$ = 2.8 Hz, $J_{5,6}$ = 9.3 Hz, 5-ArH), 9.12 (1H, d, J = 9.3 Hz, 6-ArH), 9.15 (1H, d, J = 2.8 Hz, 3-ArH), 10.7 (1H, s, NH); IR (KBr, ν_{max}, cm^{-1}): 3334 (NH), 1710 (CO), 1511 (phenyl), 1347 (CH_3); MS (m/z %): 337 (18), 225 (55), 196 (25), 155 (100), 99 (17), 85 (18), 71 (40), 57 (35), 43 (22); Anal. calcd. for $C_{16}H_{23}N_3O_5$ (m.w. 337.16): C 56.96, H 6.87, N 12.46. Found: C 57.23, H 7.12, N 12.52.

RESULTS AND DISCUSSION

The only example for the preparation of N-alkyl-2,4-dinitrophenylamine (**4**) through the reaction of 2,4-dinitrophenylamine (**1**) with alkyl halides **2**. The formation of N-propyl-2,4-dinitrophenylamine (**4a**)[1] in 48 % yield in the synthesis of 1-alkoxy-2-alkylbenzimidazoles through staggered addition of sodium hydride (3 mmol) and propyl iodide (2 mmol) to the solution of 2,4-dinitrophenylamine (**1**) (1 mmol) in THF over 12 h in the synthesis of 1-alkoxy-2-alkylbenzimidazoles. When the same reaction was carried out in acetonitrile but using propyl bromide instead of propyl iodide and under ultrasound irradiation at 40 ºC for 45 min, compound **4a** was obtained in 53.3 % yield. Further experiments showed that prolonged period of ultrasonication did not increase the yield of products. Analogous reaction of 2,4-dinitrophenylamine with alkyl halides **2b-f** under efficient and harsh mixing of ultrasound resulted in the formation of N-alkyl-2,4-dinitro-phenyamine **4b-f** in 58.5-72 % yields (**Scheme-I**).



Scheme-I

To the best of our knowledge only one report for the preparation of N-(2,4-dinitrophenyl)alkanamides **5** through acylation of, 2,4-dinitrophenylamine **1** with acyl chlorides **3** (n = 6-16) has been reported[2] in which only physico-chemical properties, spectroscopic data and yields of compounds of n = 6 (14.4 %) and n = 14 (13.5 %) are given. In our hands good-high yields (59-91 %) of some reported N-(2,4-dinitrophenyl)alkanamides **5** (n = 5-10) were obtained by the reaction of 2,4-dinitrophenylamine **1** with acylchlorides **3** (n = 4-8) in acetonitrile in the presence of sodium hydride at 40 °C for 45 min using ultrasound irradiation (**Scheme-I**).

Conclusion

By application of ultrasound irradiation in the classical methods for N-alkylation and acylation of amines several known (**4a** and **5c**) and novel N-alkyl and N-acyl 2,4-dinitrophenylamine (**4b-f** and **5a,b,d,e**) could be prepared in high yields from the cheap and readily available chemicals under mild reaction conditions and at short reaction times.

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