SYNTHESIS OF 2-ARYL-1,3-PROPANEDIAMINES USING A ONE-POT KNOEVENAGEL-MICHAEL SEQUENCE

***PATRICIO ITURRIAGA-VÁSQUEZ,[1] SUSAN LÜHR-SIERRA,[1] MARCOS CAROLI REZENDE,[2]* AND BRUCE K. CASSELS [1]**

[1] Millennium Institute for Advanced Studies in Cell Biology and Biotechnology, and Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile

[2] Departamento de Química, Facultad de Química y Biología, Universidad de Santiago, Santiago, Chile

E-mail: bcassels@uchile.cl

ABSTRACT

A simple synthetic route for the preparation of 2-phenyl-1,3-propanediamines, based on a Knoevenagel-Michael double condensation followed by reduction, was developed using nitromethane as reagent and solvent, and sodium bicarbonate as base in the first step, followed by catalytic hydrogenation over Adams catalyst.

Keywords: Knoevenagel-Michael double condensation; 2-phenyl-1,3-propanediamines; catalytic hydrogenation; Adams catalyst.

INTRODUCTION

Propanediamines are versatile building blocks for the synthesis of heterocyclic compounds. Recent reports of their use include a general method of preparation of cyclic ureas,[1] cyclic guanidines,[2] and tetrahydropyrimidines.[3] The development of libraries of propanediamines with a range of lipophilicities,[4] and the synthesis of an asymmetric member of this family for the preparation of peptidomimetics,[5] are examples of their use in combinatorial chemistry. Some propanediamines have found applications in their own right as radioprotectors or as radioactive brain-imaging agents,[6,7] and some 2-aryl-substituted derivatives have been described as potential dopaminergic agents, as ligands in coordination chemistry, and as intermediates for the synthesis of antidepressants.[8-10]

In the present report we describe a general, Knoevenagel-Michael two-step method for the preparation of 2-aryl-1,3-propanediamines (Table 2), which may serve as building blocks for a variety of heterocyclic systems. The method takes advantage of the one-pot condensation of aromatic aldehydes with two molar equivalents of nitromethane to afford the intermediate 2-aryl-1,3-dinitropropanes (Table 1), using sodium bicarbonate as catalyst. The mechanism of formation of the latter compounds and the search for a convenient basic catalyst for this conversion have been the subject of a recent report by our group.[11] Their preparation in a one-pot reaction with an inexpensive basic catalyst that can be removed by filtration represents a significant improvement over other methods.

EXPERIMENTAL

Melting points were obtained using a Kofler hot-stage apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX 300 spectrometer.

General procedure for the preparation of 2-aryl-1,3-dinitropropanes - A suspension of the appropriate aromatic aldehyde (10 mmol) and $NaHCO_3$ (30 mmol) in $MeNO_2$ (150 mL) was refluxed for 3 days until all the aldehyde had reacted, as checked by TLC. The filtered solution was concentrated under reduced pressure, and the residue purified by column chromatography (silica gel 60, 230-400 mesh), using CH_2Cl_2 as eluent to give the pure 2-aryl-1,3-dinitropropane (**2a-g**) and small amounts of the corresponding 2-hydroxy-2-arylnitroethane as side product (**1**). In this way the compounds collated in Table 1 were obtained and their identity confirmed by their ^{1}H NMR spectra, and in most cases by comparison with the data reported in the literature.[11] The properties of the new 2-(4'-methylthiophenyl)-1,3-dinitropropane are as follows:

2-(4'-Methylthiophenyl)-1,3-dinitropropane (2g), m.p. 49-51 ºC. ^{1}H NMR ($CDCl_3$) *d* 6.84 (2H, d, *J* = 7.4 Hz), 7.62 (2H, d, *J* = 7.4 Hz), 7.46 (2H, d, *J* = 7.5 Hz), 2.78 (3H, s), 4.58 (4H, m), 4.19 (1H, m). ^{13}C NMR (DMSO-d_6) δ 141.9 (C-1'), 130.4 (C-4'), 126.9 (C-2', C-6'), 125.1 (C-3', C-5'), 50.2 (C-1, C3), 43.2 (C-2), 16.8 (4'-SCH_3). Analysis calc. for $C_{10}H_{12}O_4N_2$ S C, 46.87; H 4.72; N 10.90; S 12.51; found C, 46.91; H, 4.78; N, 10.92; S, 12.49.

General procedure for the preparation of 2-aryl-1,3-diaminopropanes - A suspension of the dinitro derivative (**2a-g**, 10 mmol) and PtO_2 (30 mg) in EtOH (200 mL) was shaken under H_2 (70 psi) in a Parr hydrogenation apparatus at 25 ºC for 24 h. The filtered solution was then concentrated under reduced pressure to give 2-aryl-1,3-diaminopropanes with good yields. These were converted into the corresponding dihydrochlorides by treatment with aq. HCl in EtOH. In this way, the following dihydrochlorides of the 2-aryl-1,3-diaminopropanes (**3a-g**, see Table 2) were prepared:

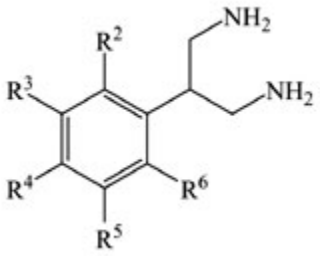

Table 2. 2-Phenyl-1,3-propanediamines prepared in this work

Compound	R^2	R^3	R^4	R^5	R^6	Yield %[a]
3a	H	H	H	H	H	73
3b	H	-OCH_2O-		H	H	46
3c	H	OCH_3	OCH_3	OCH_3	H	71
3d	H	OCH_3	OH	H	H	47
3e	H	H	$N(CH_3)_2$	H	H	81
3f	OCH_3	H	H	OCH_3	H	84
3g	H	H	SCH_3	H	H	80

[a] From the corresponding 2-aryl-1,3-dinitropropanes **2a-g**.

2-Phenyl-1,3-propanediamine . 2HCl (3a), m.p. 244-246 ºC. ^{1}H NMR (DMSO-d_6) *d* 7.32-7.20 (5H, m), 3.41 (3H, m), 3.05 (2H, m). ^{13}C NMR (DMSO-d_6) δ 143.6 (C-1'), 129.2 (C-2', C6'), 128.1 (C-3', C5'), 125.5 (C-4'), 45.61 (C-1, C-3), 40.64 (C-2).

2-(3',4'-Methylenedioxyphenyl) -1,3-propanediamine . 2HCL 2HCl (3b), m.p. 268-270 ºC. ^{1}H NMR (DMSO-d_6) δ 6.79 (1H, s), 6.56 (2H, m), 5.96 (2H, s), 3.72 (4H, m), 3.23 (1H, m). ^{13}C NMR (DMSO-d_6) δ 147.0 (C-3'), 146.1 (C-4'), 134.3 (C-1'), 123.4 (C-6'), 109.9 (C-2'), 108.3 (C-5'), 100.9 (*O*-CH_2-*O*), 45.61 (C-1, C-3), 41.83 (C-2). Analysis calc. for $C_{10}H_{16}Cl_2N_2O_2$ C, 44.96; H, 6.04; Cl, 26.24; N, 10.49; found C, 45.16; H, 6.14; Cl, 26.20; N, 10.57.

2-(3',4',5'-Trimethoxyphenyl) -1,3-propanediamine . 2HCL 2HCl (3c), m.p. 248-250ºC. ^{1}H NMR (DMSO-d_6) δ 6.72 (2H, s), 3.84 (6H, s), 3.73 (3H, s), 3.77 (4H, m), 3.26 (1H, m). ^{13}C NMR (DMSO-d_6) δ 152.0 (C-3', C-5'), 139.1 (C-1'), 136.1 (C-4'), 105.7 (C-2', C6'), 60.7 (4'-*O*-CH_3), 56.2 (3'-*O*-CH_3, 4'-*O*-CH_3), 46.9 (C-2), 45.6 (C-1, C-3). Analysis calc. for $C_{11}H_{20}Cl_2N_2O_3$ C, 44.16; H, 6.74; Cl, 23.60; N, 9.36; found C 44.26, H, 6.79, Cl, 23.58; N, 9.26.

2-(3'-Methoxy-4'-hydroxyphenyl) -1,3-propanediamine . 2HCL 2HCl (3d), m.p. 262 ºC (decomp.). ^{1}H NMR (DMSO-d_6) δ 8.51 (1H, s), 6.92 (1H, d, *J* = 7.5 Hz), 6.89 (1H, s), 6.70 (1H, d, *J* = 7.5 Hz), 3.66 (4H, m), 3.46 (1H, m). ^{13}C NMR (DMSO-d_6) δ 147.2 (C-3'),

142.0 (C-4'), 134.3 (C-1'), 123.7 (C-6'), 115.9 (C-5'), 114.8 (C-2'), 55.94 (3'-*O*-CH_3), 45.61 (C-1, C-3), 41.83 (C-2). Analysis calc. for $C_{10}H_{18}C_{l2}N_2O_2$ C, 44.62; H, 6.74; Cl, 26.34; N, 10.41; found C, 44.59; H, 6.86; Cl, 26.45; N, 10.58.

2-(4'-Dimethylaminophenyl) mine . 2HCL-1,3-propane-diamine 2HCl (3e), m.p. 188-198 ºC. ^{1}H NMR (DMSO-d_6) δ 8.12 (2H, d, J = 8.6 Hz), 7.42 (2H, d, J = 8.5 Hz), 3.41 (4H, m), 3.26 (1H, m), 3.05 (6H, s). ^{13}C NMR (DMSO-d_6) δ 148.3 (C-4'), 132.3 (C-1'), 130.6 (C-2', C-6'), 111.3 (C-3', C-6'), 45.61 (C-1, C3), 40.64 (C-2), 40.48 (4'-*N*-CH_3).`Analysis calc. for`$C_{11}H_{21}Cl_2N_3$ C, 49.63; H, 7.95; Cl, 26.63; N, 15.78; found C, 49.55; H, 7.99; Cl 26.62; N, 15.84.

2-(2',5'-Dimethoxyphenyl) -1,3-propanediamine . 2HCL 2HCl (3f), m.p. 161-162 ºC. ^{1}H NMR (DMSO-d_6) δ 6.96 (1H, d, J = 8.7 Hz), 6.87 (2H, m), 3.76 (3H, s), 3.72 (3H, s), 3.31 (4H, m), 3.08 (1H, m). ^{13}C NMR (DMSO-d_6) δ 153.4 (C-5'), 151.7 (C-2'), 129.1 (C-1'), 114.8 (C-6'), 114.7 (C-3'), 112.7 (C-4'), 56.31 (5'-*O*-CH_3), 55.23 (2'-*O*-CH_3), 45.96 (C-1, C-3), 39.29 (C-2). Analysis calc. for $C_{11}H_{20}Cl_2N_2O_2$ C, 46.65; H, 7.12; Cl, 25.04; N, 9.89; found C, 46.68; H, 7.37; Cl, 24.97; N, 9.99.

2-(4'-Methylthiophenyl)-1,3-propanediamine . 2HCL 2HCl (3g), m.p. 254-258 ºC. ^{1}H NMR (DMSO-d_6) δ 7.52 (2H, d, J = 7.6 Hz), 7.40 (2H, d, J = 7.5 Hz), 2.76 (3H, s), 3.38 (4H, m), 3.19 (1H, m). ^{13}C NMR (DMSO-d_6) δ 141.6 (C-1'), 133.4 (C-4'), 129.1 (C-2', C-6'), 126.8 (C-3', C-5'), 45.65 (C-1, C3), 40.64 (C-2), 15.90 (4'-*S*-CH_3). Analysis calc. for $C_{10}H_{18}Cl_2N_2$ S C, 44.61; H, 6.74; Cl, 26.34; N, 10.40; S, 11.91; found C, 44.47; H, 6.85; Cl, 26.45; N, 10.50; S, 11.83.

RESULTS AND DISCUSSION

The one-pot tandem condensation of aromatic aldehydes with nitromethane in the presence of sodium bicarbonate, using excess nitromethane as solvent, gave the 2-aryl-1,3-dinitropropanes in acceptable to good yields, although three days were required for the reactions to reach completion. The Knoevenagel-Michael reactions failed in protic solvents, *i.e.* ethanol and methanol, in which the 2-nitro-1-phenylethanols (the side products) were formed in high yields, and in acetic acid, in which the corresponding phenylnitroethenes were the main reaction products. The mild conditions reported here required longer reaction times, but minimized the formation of side products. Thus, the isolated yields of 2-aryl-1,3-dinitropropanes **2a-g** prepared by this method, as compared with the original description using butylamine as catalyst (Table 1),[12] are similar or better in some cases although they have not been optimized.

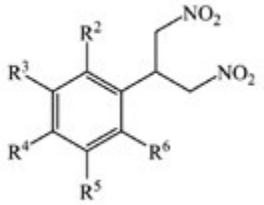

Table 1. 2-Phenyl-1,3-dinitropropanes prepared in this work

Compound	R^2	R^3	R^4	R^5	R^6	Yield %[a]	Yield %[b]
3a	H	H	H	H	H	53	45
3b	H	-OCH_2O-		H	H	24	52
3c	H	OCH_3	OCH_3	OCH_3	H	51	31
3d	H	OCH_3	OH	H	H	28	65
3e	H	H	$N(CH_3)_2$	H	H	66	68
3f	OCH_3	H	H	OCH_3	H	78	–
3g	H	H	SCH_3	H	H	64	–

[a] The present work, using $NaHCO_3$ as catalyst.

[b] Using $BuNH_2$ as catalyst.[12]

The dinitro derivatives were reduced to the corresponding 1,3-propanediamines **3a-g** using catalytic hydrogenation over Adams catalyst in a Parr shaking apparatus. Other hydrogenation catalysts such as Pd-C 5-10 % and Raney nickel only gave low yields of the 2-aryl-1,3-propanediamines (figure 1). The pressure in the Parr reactor was controlled and maintained at 70 psi for the duration of the reaction, as the rates and yields of this kind of reaction are pressure-dependent. Catalytic reduction proved to be more effective than the classical reduction with metals (*i.e.* Sn^0) in acid medium, where the work-up was the limiting operation leading to considerably lower yields.

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