

Synthesis of Some 2-Aminonitroethanes *via* Silica Gel-Catalyzed Nitro-Mannich Reaction

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A direct one pot, three-component nitro-Mannich reaction of a nonenolizable aldehyde, aniline or one of its ring-substituted derivatives and nitromethane was carried out on silica gel surface. The products of the reaction, 2-aminonitroethane, were obtained in high yields. IR, ^1H NMR, ^{13}C NMR spectra and elemental analysis confirmed the structures of the products.

Key words: Nitro-Mannich Reaction, Nonenolizable Aldehydes, Imines

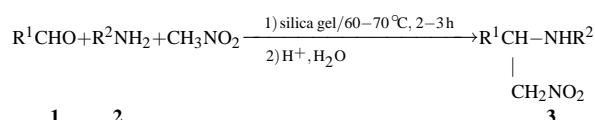
Introduction

One of the earliest C-C bond formation reaction methodologies was the Mannich reaction or more generally the α -aminoalkylation of carbonyl compounds. The reaction involves an aldehyde, usually formaldehyde, the salt of an amine and a C-H acid, a ketone or nitroalkane in a protic solvent such as ethanol. The reaction mixture is then refluxed for several days after which the product is isolated in widely varying yields [1]. The conventional Mannich reaction, however, has serious drawbacks such as drastic reaction conditions (high temperature, long reaction time, and use of protic solvents) all leading to undesirable by-products.

In this paper, a one-pot three-component nitro-Mannich type reaction catalyzed by silica is reported. The reaction occurred smoothly at mild conditions giving high yields of 2-aminonitroethane products. Similar products were obtained *via* a tin(II) chloride mediated addition reaction of bromonitromethane to imines [2]. Short reaction time, ease of handling the reaction and low cost of substances are the advantages of the described method here over other methods.

Results and Discussion

2-Amino-1-nitroethanes **3** were obtained from aldehydes **1**, anilines **2**, and nitromethane on silica gel surface in high yields (Scheme 1, Table 1). For example, when benzaldehyde, 4-methylaniline, nitromethane and silica gel were heated in a pressure tube for 80 min, compound **3d** was obtained in 90% yield.



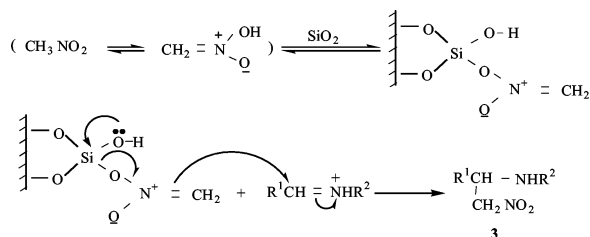
Scheme 1.

Table 1. Yields of product **3**.

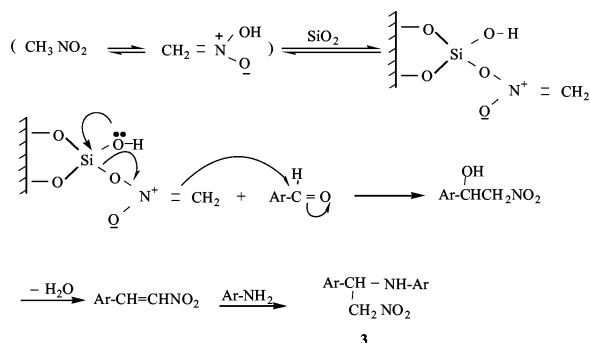
3	R¹	R²	Yield [%]
a	2-Methyl-C ₆ H ₄	4-Bromo-C ₆ H ₄	85
b	4-Ethyl-C ₆ H ₄	4-Nitro-C ₆ H ₄	82
c	3-Nitro-C ₆ H ₄	C ₆ H ₅	80
d	C ₆ H ₅	4-Methyl-C ₆ H ₄	90
e	4-Hydroxy-C ₆ H ₄	C ₆ H ₅	87
f	2,4-Dichloro-C ₆ H ₃	C ₆ H ₅	77
g	4-Methoxy-C ₆ H ₄	4-Nitro-C ₆ H ₄	83
h	1-Naphthyl	C ₆ H ₅	78
i	2-Naphthyl	4-Bromo-C ₆ H ₄	87
j	H	C ₆ H ₅	95
k	H	4-Bromo-C ₆ H ₄	90
l	H	4-Nitro-C ₆ H ₄	92
m	H	4-Methyl-C ₆ H ₄	88

The ^1H NMR spectrum of product **3d** shows a broad signal at $\delta = 4.23$ for the NH proton which could be quenched with deuterium oxide, a doublet at $\delta = 4.72$ (CH_2NO_2) and a triplet at $\delta = 5.30$ (benzylic CH). The ^{13}C NMR spectrum showed characteristic signals at $\delta = 56.8$ (benzylic carbon) and 80.5 ppm (CH_2NO_2). The compound showed a strong IR absorption at 1552 cm^{-1} for the NO_2 group. All other prepared products gave ^1H NMR, ^{13}C NMR and IR signals consistent with the assigned structures.

It has been generally known that the reaction pathways of the Mannich reaction depend on the nucleophilicity of substrate and the pH of the re-



Scheme 2.



Scheme 3.

action medium [3]. The mechanism of the silica-catalyzed nitro-Mannich reaction described here is not known, however, a proposed mechanism, as shown in Scheme 2, is suggested. This mechanism involves reaction of nitromethane or its aci-nitro (nitronic) acid form with the Si = O double bond at the surface of silica as a first step [4]. A nucleophilic attack of the product on imine or imonium ions that are formed during the course of the reaction to give product **3** and regenerates the catalyst is the second step.

An alternative mechanism involving two steps could also be proposed Scheme 3. The first step is a silicagel-catalyzed aldol-type condensation forming nitrostyrene and addition of amine to the latter to form product **3** in the second step.

Conclusion

As can be seen from the results the method described here can be considered as an efficient method for this kind of C-C bond formation reaction. Functionalities present in the products may be suitable for a wide range of other chemical manipulations. The CH₂NO₂ unit, for example, can be transformed into a carbonyl group by the Nef reaction [5], and then to carboxylic acid, making products **3** precursors to some α -amino acids. The feasibility of replacing the nitro group by hydrogen atom (denitration) using tributyltin hydride is also important [6].

Experimental Section

All reagents were of commercial grade, and reagent quality solvents were used without further purification. IR spectra were determined on a Mattson 5000 spectrometer. NMR spectra were determined on Bruker AC 200 MHz instrument. In all cases, samples were dissolved in CDCl₃ using TMS as internal standard. The elemental analysis was performed at the Middle East Technical University Analyses Center.

General procedure for the synthesis of **3a–3i**

Into a pressure tube silica gel (0.50 g, Scharlau for thin layer chromatography with gypsum and pigment addition for UV) together with nitromethane (2.5 mmol) was introduced. Aromatic aldehyde (2.5 mmol) and aniline or its ring-substituted derivative (2.5 mmol) were also introduced. When either the aldehyde or the aniline derivative or both were solids they were boiled with THF (1 ml) and the solvent was evaporated to dryness before silica gel and nitromethane were added. The tube was then closed and immersed into an oil bath where the temperature was kept at 60–70 °C. The reaction was monitored by TLC, ethyl acetate / hexane mixture 1 : 5 was used as eluent. It was found that the reaction was about 80% complete after the first 20 min.

After 2–3 h the contents of the tube were extracted with ethyl acetate (30 ml). The extract was successively washed with 3 × 20 ml portions of 1 M HCl solution, saturated aqueous NaHCO₃ (20 ml) solution and brine (20 ml). The solution was then dried over anhydrous MgSO₄. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, ethyl acetate / hexane mixture 1 : 4 as eluent).

General procedure for the synthesis of **3j–3m**

Paraformaldehyde (2.5 mmol), aniline or its ring-substituted derivative (2.5 mmol) and dry THF (1 ml) were boiled in a pressure tube until no solid was observed. Silica gel 0.50 g and nitromethane (2.5 mmol) were introduced. The tube was closed and immersed in an oil bath at 60–70 °C. The reaction was completed as before and also the workup and purification procedures were similar.

2-(4-Bromoanilino)-2-(2-methylphenyl)-1-nitroethane (3a): M. p. 101–103 °C. – IR (KBr): ν = 3399 (N-H), 3073, 3019, 2920, 1591, 1547 (NO₂), 1495, 1381, 1256, 1182, 1072 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 2.48 (s, 3H, Me), 4.38 (broad, 1H, NH), 4.61 (m, 2H, CH₂NO₂), 5.30 (m, 1H, *o*-CH₃-C₆H₄CH), 6.32–7.42 (m, 8H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 19.3 (Me), 53.3 (*o*-CH₃-C₆H₄CH), 78.3 (CH₂NO₂), 110.5, 115.2, 125.2, 127.0, 128.8, 131.3, 132.0, 134.8, 135.4, 144.4 (Ar). – C₁₅H₁₅N₂O₂Br (335.20): calcd. C 53.74, H 4.51, N 8.36; found C 53.61, H 4.55, N 8.40.

2-(4-Nitroanilino)-2-(4-ethylphenyl)-1-nitroethane (3b): M.p. 96–97 °C. – IR (KBr): ν = 3399 (N-H), 3329, 2962, 2929, 2898, 1601, 1554 (NO₂), 1477, 1300, 1184, 1111 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 1.21 (t, ³J = 4 Hz, 3H, CH₃CH₂), 2.63 (q, ³J = 4 Hz, 2H, CH₃CH₂), 4.80 (m, 2H, CH₂NO₂), 5.31 (m, 1H, p-C₂H₅-C₆H₄CH), 5.72 (broad, 1H, NH), 6.53–8.8 (m, 8H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 15.5 (CH₃CH₂), 28.8 (CH₃CH₂), 56.0 (p-C₂H₅-C₆H₄CH), 80.0 (CH₂NO₂), 112.5, 113.3, 126.1, 126.3, 129.5, 133.0, 145.5, 151.8 (Ar). – C₁₆H₁₇N₃O₄(315.32): calcd. C 60.94, H 5.43, N 13.33; found C 60.77, H 5.45, N 13.42.

2-Anilino-2-(3-nitrophenyl)-1-nitroethane (3c): M.p. 126–128 °C (lit. 127–128 °C). – IR (KBr): ν = 3404 (N-H), 2924, 2854, 1602, 1554, 1529 (NO₂), 1352, 1313, 1293 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 4.63 (broad, 1H, NH), 4.72 (d, ³J = 4 Hz, 2H, CH₂NO₂), 5.28 (q, ³J = 4 Hz, 1H, C₆H₄CH), 6.50–8.32 (m, 9H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 56.0 (C₆H₄CH), 79.7 (CH₂NO₂), 114.0, 119.6, 122.0, 124.0, 129.5, 130.2, 132.9, 140.2, 145.0, 149.0 (Ar). – C₁₄H₁₃N₃O₄ (287.27): calcd. C 58.53, H 4.56, N 14.63; found C 58.44, H 4.47, N 14.66.

2-(4-Methylanilino)-2-phenyl-1-nitroethane (3d): M.p. 83–84 °C (lit. 82–84 °C). – IR (KBr): ν = 3409 (N-H), 3028, 2920, 1618, 1552 (NO₂), 1520, 1452, 1379, 1302, 1259 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 2.25 (s, 3H, Me), 4.23 (broad, 1H, NH), 4.72 (d, ³J = 5 Hz, 2H, CH₂NO₂), 5.30 (t, ³J = 5 Hz, 1H, C₆H₅CH), 6.35–7.50 (m, 9H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 20.5 (Me), 56.8 (C₆H₅CH), 80.5 (CH₂NO₂), 114.0, 126.5, 128.8, 129.5, 130.0, 132.0, 138.0, 143.8 (Ar). – C₁₅H₁₆N₂O₂ (256.29): calcd. C 70.29, H 6.29, N 10.93; found C 70.33, H 6.32, N 10.88.

2-Anilino-2-(4-hydroxyphenyl)-1-nitroethane (3e): M.p. 109–110 °C. – IR (KBr): ν = 3410 (N-H), 3379 (OH), 2924, 2845, 1604, 1541 (NO₂), 1504, 1431, 1384, 1315, 1295, 1222, 1129 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 3.72 (broad, 1H, NH), 4.35 (s, 1H, OH), 4.72 (d, ³J = 5 Hz, 2H, CH₂NO₂), 5.21 (m, 1H, C₆H₄CH), 6.6–8.12 (m, 9H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 56.1 (C₆H₄CH), 80.3 (CH₂NO₂), 113.8, 116.0, 116.5, 119.0, 128.0, 129.3, 132.0, 139.2 (Ar). – C₁₄H₁₄N₂O₃ (258.27): calcd. C 65.10, H 6.46, N 10.85; found C 65.44, H 6.32, N 10.89.

2-Anilino-2-(2,4-dichlorophenyl)-1-nitroethane (3f): M.p. 112–114 °C. – IR (KBr): ν = 3402 (N-H), 3055, 2924, 1605, 1554 (NO₂), 1504, 1423, 1379, 1311, 1263, 1101, 1045 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 4.20 (broad, 1H, NH), 4.70 (m, 2H, CH₂NO₂), 5.53 (m, 1H, 2,4-Cl₂-C₆H₃CH), 6.54–7.53 (m, 8H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 53.1 (2,4-Cl₂-C₆H₃CH), 78.5 (CH₂NO₂), 114.0, 119.5, 121.2, 128.0, 129.1, 129.4, 129.5, 133.5, 135.2, 145.0 (C₆H₄). – C₁₄H₁₂N₂O₂Cl₂(311.15):

calcd. C 54.06, H 3.89, N 9.00; found C 54.11, H 3.90, N 9.11.

2-(4-Nitroanilino)-2-(4-methoxyphenyl)-1-nitroethane (3g): M.p. 115–117 °C. – IR (KBr): ν = 3383 (N-H), 1601, 1554 (NO₂), 1309, 1251, 1178, 1113 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 3.78 (s, 3H, OCH₃), 4.50 (broad, 1H, NH), 4.75 (d, 2H, ³J = 5 Hz, 2H, CH₂NO₂), 5.25 (q, 1H, ³J = 5 Hz, CH₃O-C₆H₄CH), 6.6.52–8.22 (4 d, 8H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 55.1 (OCH₃), 55.2 (CH₃O-C₆H₄CH), 79.8 (CH₂NO₂), 112.8, 115.0, 121.5, 128.0, 131.5, 139.8, 151.4, 160.2 (Ar). – C₁₅H₁₅N₃O₅ (317.29): calcd. C 56.68, H 4.77, N 13.24; found C 56.55, H 4.82, N 13.20.

2-Anilino-2-(1-naphthyl)-1-nitroethane (3h): M.p. 111–112 °C. – IR (KBr): ν = 3387 (N-H), 3065, 2916, 1602, 1554 (NO₂), 1512, 1425, 1373, 1315, 1265 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 4.55 (broad, 1H, NH), 4.8 (m, 2H, CH₂NO₂), 6.05 (m, 1H, C₁₀H₇CH), 6.50–8.25 (m, 12H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 52.8 (C₁₀H₇CH), 79.5 (CH₂NO₂), 113.7, 119.2, 121.8, 124.0, 125.8, 126.5, 127.5, 129.0, 129.1, 129.7, 130.8, 132.5, 134.0, 145.5 (Ar). – C₁₈H₁₆N₂O₂ (292.33): calcd. C 73.95, H 5.52, N 9.58; found C 73.88, H 5.48, N 9.62.

2-(4-Bromoanilino)-2-(2-naphthyl)-1-nitroethane (3i): M.p. 111–112 °C. – IR (KBr): ν = 3408 (N-H), 2924, 2852, 1595, 1553 (NO₂), 1498, 1377, 1330, 1082 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 4.60 (broad, 1H, NH), 4.78 (m, 2H, CH₂NO₂), 5.30 (m, 1H, C₁₀H₇CH), 6.45–7.92 (m, 11 H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 57.2 (C₁₀H₇CH), 80.0 (CH₂NO₂), 110.8, 115.5, 123.9, 126.0, 126.8, 128.0, 128.0, 128.2, 129.9, 142.2, 133.3, 134.7, 139.5, 145.0 (Ar). – C₁₈H₁₅N₂O₂Br (371.22): calcd. C 58.24, H 4.07, N 7.55; found C 58.33, H 4.10, N 7.48.

2-Anilino-1-nitroethane (3j): Oil. – IR (KBr): ν = 3400 (N-H), 2924, 2854, 1602, 1550 (NO₂), 1510, 1427, 1384, 1317, 1257 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 3.75 (t, ³J = 4.0 Hz, 2H, NHCH₂), 4.06 (broad, 1H, NH), 4.55 (t, ³J = 4.0 Hz, 2H, CH₂NO₂), 6.57–7.30 (m, 5 H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 41.5 (NHCH₂), 74.2 (CH₂NO₂), 113.0, 119.0, 129.4, 146.5 (Ar). – C₈H₁₀N₂O₂ (166.18): calcd. C 57.82, H 6.07, N 16.86; found C 57.77, H 6.10, N 16.77.

2-(4-Bromoanilino)-1-nitroethane (3k): M.p. 41–42 °C. – IR (KBr): ν = 3400 (N-H), 2854, 1593, 1537 (NO₂), 1498, 1427, 1358, 1317, 1248, 1180 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 3.77 (t, ³J = 4.7 Hz, 2H, NHCH₂), 4.16 (broad, 1H, NH), 4.57 (t, ³J = 4.7 Hz, 2H, CH₂NO₂), 6.57, 7.30 (2 d, ³J = 8.5 Hz, 4 H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): δ = 41.1 (NHCH₂), 74.4 (CH₂NO₂), 110.7, 114.8, 132.4, 146.0 (Ar). – C₈H₉N₂O₂Br (245.07): calcd. C 39.21, H 3.70, N 11.43; found C 39.27, H 3.74, N 11.47.

2-(4-Nitroanilino)-1-nitroethane (3l): M. p. 82–83 °C. – IR (KBr): $\nu = 3371$ (N-H), 1628, 1547 (NO₂), 1479, 1284, 1182, 1111 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): $\delta = 3.92$ (t, ³J = 4.7 Hz, 2H, NHCH₂), 4.14 (broad, 1H, NH), 4.65 (t, ³J = 4.7 Hz, 2H, CH₂NO₂), 6.60, 8.12 (2 d, ³J = 8.5 Hz, 4 H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): $\delta = 40.5$ (NHCH₂), 74.0 (CH₂NO₂), 111.7, 114.5, 127.0, 148.0 (Ar). – C₈H₉N₃O₄ (221.18): calcd. C 45.50, H 4.30, N 19.89; found C 45.44, H 4.27, N 19.77.

2-(4-Methylanilino)-1-nitroethane (3m): M. p. 72–73 °C. – IR (KBr): $\nu = 3396$ (N-H), 2922, 1614, 1537 (NO₂), 1427, 1356, 1319, 1251, 1197 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): $\delta = 2.23$ (s, 3 H, Me), 3.78 (t, ³J = 4.7 Hz, 2H, NHCH₂), 3.95 (broad, 1H, NH), 4.58 (t, ³J = 4.7 Hz, 2H, CH₂NO₂), 6.58, 7.30 (2 d, ³J = 8.5 Hz, 4 H, Ar). – ¹³C{H} NMR (200 MHz, CDCl₃): $\delta = 20.6$ (Me), 41.5 (NHCH₂), 74.3 (CH₂NO₂), 114.8, 128.0, 129.70, 143.0 (Ar). – C₈H₁₂N₂O₂ (180.20): calcd. C 59.99, H 6.71, N 15.55; found C 59.85, H 6.73, N 15.45.

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