Nitroalkanes as a New, Convenient Source of 1-Acyl-2,5-dialkylbenzene Derivatives, in Two Steps

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Received April 25, 2000

Introduction

Nitroalkanes have proved to be valuable intermediates.[1] Both the activating effect of the nitro group and its facile transformation into various functionalities have extended the importance of nitro compounds in the preparation of complex molecules.[2] Peculiar to aliphatic nitro compounds is the formation of new carbon−carbon single bonds, via the nitronate[3] and, in specific cases, the creation of carbon−carbon double bonds through the elimination of nitrous acid.[4] Recently, we disclosed that nitroalkanes exhibit a remarkable reactivity in water,[5] in particular their conjugate addition to electron-deficient alkenes.[5a,c] On the basis of these considerations, we have found that nitroalkanes can be conveniently used as building blocks to produce aromatic systems.

Aromatization of acyclic precursors is undoubtedly a useful reaction in the synthesis of highly substituted aromatic rings,[6] and although several methods to obtain aromatic compounds are known,[7] to the best of our knowledge the use of nitroalkanes in the synthesis of substituted benzenes has not been reported.[8] The nucleophilicity of nitroalkanes and the ability of the nitro-functionality to act as a leaving group[4] make possible a simple and practical synthesis of 1-acyl-2,5-dialkylbenzene derivatives in two steps.

Results and Discussion

The first step of our procedure was the double Michael addition, in aqueous medium, of the nitroalkanes **1** to the enones **2**, followed by in situ intramolecular aldol reaction of the adducts **3** (Scheme 1). The cyclohexanols **4** were obtained in 70−95% yield as a diastereomeric mixture. After workup, the compounds **4** and a stoichiometric amount of TsOH were dissolved in toluene and refluxed with a Dean−Stark apparatus, with the simultaneous injection of air. Thus, the aromatic compounds **7** were obtained directly in 50−80% yield. The conversion of **4** to **7** proceeds initially through the elimination of both water (compounds **5**) and nitrous acid, leading to the compounds **6**, which convert, by air oxidation, to the aromatic systems **7**. The formation of the intermediates **5** and **6** was detected by GC−MS during the reaction.

It is important to point out that since the acetyl derivatives **7** (R^1 = Me) can be easily converted into phenols (Baeyer−Villiger rearrangement)[9] or carboxylic acids (haloform reaction),[10] they are potential precursors of 2,5-dialkylphenols and 2,5-dialkylbenzoic acids, both important targets widely used for industrial[11] and pharmaceutical applications.[12,13]

Our procedure allows the preparation of aromatic systems from open-chain compounds in satisfactory to good yields (Table 1). Moreover, several advantages can be seen in this approach, such as the preparation of trisubstituted compounds in only two steps and the avoidance of *ortho*−*meta*−*para* mixture formation common in conventional aromatic synthesis. In fact, our method appears as a regiodefined synthesis of 1-acyl-2,5-dialkylbenzenes very difficult to prepare by electrophilic substitution of benzenes. These compounds were usually prepared from 1,4-disubstituted benzenes, and while the acylation of symmetric 1,4-dialkylbenzenes does not present complications[14] of regioselectivity, more problematic is the acylation of nonsymmetric 1,4-dialkylbenzenes.[15] Moreover, in our method the appropriate choice

(1) (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *31*, 1−18. (b) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833−847. (c) Ballini, R. *Synlett* **1999**, 1009−1018.

(2) (a) Stach, H.; Hesse, M. *Tetrahedron* **1988**, *44*, 1573−1590. (b) Ballini, R. In *Studies in Natural Products Chemistry;* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1997; Vol. 19, pp 117−184.

(3) (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 321−340. (b) Ballini, R.; Marziali, P.; Mozzicafreddo, A. *J. Org. Chem*. **1996**, *61*, 3209−3211 and references cited therein.

(4) See for example: (a) Seebach, D.; Hoekstra, M. S.; Protschuk, G. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 321−322. (b) Ono, N.; Yanai, T.; Hamamoto, I.; Kamimura, A.; Kaji, A. *J. Org. Chem*. **1985**, *50*, 2806−2807. (c) Kitahara, T.; Mori, K. *Tetrahedron* **1984**, *40*, 2935−2944. (d) Yamashita, M.; Tamada, Y.; Iida, A.; Oshikawa, T. *Synthesis* **1990**, 420−422. (e) Ballini, R.; Rinaldi, A. *Tetrahedron Lett*. **1994**, *35*, 9247−9250. (f) Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213−4222. (g) Kostova, K.; Hesse, M. *Helv. Chim. Acta* **1995**, *78*, 440−446. (h) Vanelle, P.; Terme, T.; Maldonado, J.; Crozet, M. P.; Giraud, L. *Synlett* **1998**, 1067−1068. (h) Kálai, T.; Jekö, M. J.; Hideg, K. *Synthesis* **1999**, 973−980. (i) Areces, P.; Gil, M. V.; Higes, F. J.; Román, E.; Serrano, J. A. *Tetrahedron Lett*. **1998**, *39*, 8557−8560. (j) Fumoto, Y.; Eguchi, T.; Uno, H.; Ono, N. *J. Org. Chem*. **1999**, *64*, 6518−6521.

(5) (a) Ballini, R.; Bosica, G. *Tetrahedron Lett*. **1996**, *37*, 8027−8030. (b) Ballini, R.; Bosica, G. *J. Org. Chem*. **1997**, *62*, 425−427. (c) Ballini, R.; Bosica, G. *Eur. J. Org. Chem*. **1998**, 355−357. (d) Ballini, R.; Papa, F.; Abate, C. *Eur. J. Org. Chem*. **1999**, 87−90.

(6) Gordon, P. F. *Chem. Soc. Rev.* **1984**, 441−488.

(7) Larock, R. C. *Comprehensive Organic Transformations*, 2nd Ed.; Wiley-VCH: New York, 1999; pp 187−213.

(8) Only the formation of nitrobenzenes via reaction of pyrylium salts with nitromethane has previously been reported: (a) Dimroth, K. *Angew. Chem*. **1960**, *72*, 331−342. (b) Dimroth, K.; Wolf, K. H. *Newer Methods Prep. Org. Chem*. **1964**, *3*, 357−423.

(9) (a) McKillop, A.; Tarbin, J. A. *Tetrahedron* **1987**, *43*, 1753−1758. (b) Token, K.; Hirano, K.; Yokoyama, T.; Goto, K. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 2766−2771. (c) Pande, C. S.; Jain, N. *Synth. Commun*. **1989**, *19*, 1271−1279. (d) Koch, S. S. C.; Chamberlin, A. R. *Synth. Commun*. **1989**, *19*, 829−833. (e) Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Gazz. Chim. Ital*. **1989**, *119*, 249. (f) Fermin, M. C.; Bruno, J. W. *Tetrahedron Lett*. **1993**, *34*, 7545−7548.

(10) (a) Neudeck, H. M. *Monatsh. Chem*. **1996**, *127*, 185−200. (b) Madler, M. M.; Klucik, J.; Soell, P. S.; Brown, C. W.; Liu, S.; Berlin, K. D.; Benbrook, D. M.; Birckbichler, P. J.; Nelson, E. C. *Org. Prep. Proced. Int*. **1998**, *30*, 230−234. (c) Kajigaeshi, S.; Nakagawa, T.; Nagasaki, N.; Fujisaki, S. *Synthesis* **1985**, 674−675.

(11) (a) Tsukise, B.; Sakamoto, H. Jpn. Kokai Tokkyo Koho JP 11,-130,712, 1999; *Chem. Abstr*. **1999**, *131*, 5091. (b) Ichikawa, K.; Ozaki, H. Jpn. Kokai Tokkyo Koho JP 09,110,757; *Chem. Abstr*. **1997**, *127*, 33979.

(12) Liao, Y.; Wang, B. *Bioorg. Med. Chem. Lett*. **1999**, 1795−1800.

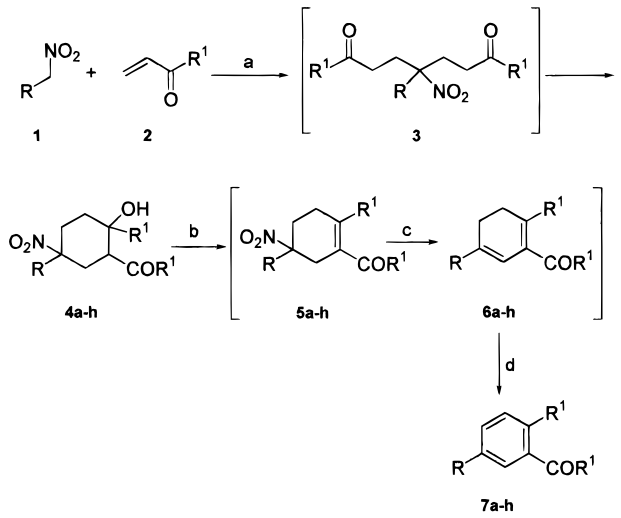
(13) Melnick, M.; Reich, S. H.; Lewis, K. K.; Mitchell, L. J., Jr.; Nguyen, D.; Trippe, A. J.; Dawson, H.; Davies, J. F., II; Appelt, K.; Wu, B.-W.; Musik, L.; Gehlhaar, D. K.; Webber, S.; Shetty, B.; Kosa, M.; Kahil, D.; Andrada, D. *J. Med. Chem*. **1996**, *39*, 2795−2811.

(14) (a) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett*. **1995**, *36*, 409−412. (b) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 2053−2056. (c) Kawada, A.; Mitamura, S.; Kobayashi, S. *J. Chem. Soc., Chem. Commun*. **1996**, 183−184.

(15) Taylor, E. P.; Watts, G. E. *J. Chem. Soc.* **1952**, 1123−1127.

10.1021/jo0006324 CCC: $19.00
Published on Web 08/25/2000

Scheme 1[a]



[a] Conditions: (a) K_2CO_3, water, rt to −60 °C, 24 h, 70−95%; (b) PhMe, reflux, air, 3−15 h, $-H_2O$; (c) $-HNO_2$; (d) $-H_2$, 50−80% from **4**.

Table 1. Synthesis of Aromatic Derivatives 7

	R	R^1	yield (%) of **4** from **1**	yield (%) of **7** from **4**
a	Me	Me	90[a]	53[c]
b	Et	Me	85[a]	55[c]
c	*n*-Pr	Me	93[a]	65[c]
d	*n*-Bu	Me	95[b]	72[c]
e	*n*-C_5H_{11}	Me	95[b]	61[c]
f	*i*-Pr	Me	75[b]	50[c]
g	Ph	Me	70[b]	80[d]
h	Me	Et	77[b]	50[c]

[a] Reaction performed at rt. [b] Reaction performed at 60 °C. [c] Reaction time 15 h. [c] Reaction time 3 h.

of the starting nitroalkane and/or the alkyl vinyl ketone offers the opportunity to predict the relative positions of the substituents. Finally, the reported synthesis permits the insertion of several *n*-alkyl groups without the isomerization problems typical of the classical Friedel−Crafts alkylation. It should be noted that the synthesis of substituted biphenyls (compound **7g**) can also be accomplished.

Experimental Section

All ^{1}H NMR spectra were collected on a 300 MHz NMR spectrometer in $CDCl_3$ or DMSO-d_6. ^{13}C NMR were recorded at 75.4 or 50 MHz with $CDCl_3$ or DMSO-d_6 as reference. All mass spectra were determined on a capillary GC/MS operating in the split mode with helium carrier gas and fitted with a mass-selective detector (MSD). The column used was a HP5 capillary column, 30 m × 0.25 mm, with a 0.25 μm film thickness of 5% phenylmethylsilicone gum. The temperature of 65 °C was maintained for 3 min and then ramped at 15 °C min^{-1} to 300 °C. The products were purified by flash chromatography on Merck silica gel (0.040−0.063 mm). The enones **2** were commercially available; the nitroalkanes **1** (R = Me, Et, *n*-Pr, *n*-Bu, *n*-C_5H_{11}) were commercially available or prepared[16,17] (R = *i*-Pr, Ph) by standard procedures.

General Procedure for the Preparation of Aromatic Compounds 7a−h. Nitroalkane **1** (2 mmol) and K_2CO_3 (0.138 g, 1 mmol) were dissolved in H_2O (10 mL), then the solution was cooled with an ice bath and the conjugated enone **2** (0.42 g, 5 mmol) was added. After the resulting solution was stirred at the appropriate temperature (rt or 60 °C, Table 1) for 24 h, the aqueous medium was extracted with Et_2O (3 × 15 mL) and the organic phase was dried ($MgSO_4$). After flash chromatography purification, the diastereomeric mixture **4** was dissolved in 20 mL of toluene, TsOH (2 mmol) was added, and the reaction mixture was refluxed for the appropriate time (3−15 h, Table 1) with a Dean−Stark apparatus, with the simultaneous injection of air. The solvent was then removed under reduced pressure and the residue dissolved in EtOAc and water. After separation of the organic layer, the aqueous solution was extracted three times with EtOAc, and the combined organic solvents were dried (Na_2SO_4) and removed under reduced pressure. The crude product was chromatographed on silica gel using EtOAc/*n*-hexane (49:1) as eluent.

Data for 1-(2,5-Dimethylphenyl)-1-ethanone (7a):[18] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 2.35 (s, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 7.11 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.15 (dd, ^3J(H,H) = 7.8, ^4J(H,H) = 1.5 Hz, 1H), 7.47 (d, ^4J(H,H) = 1.5 Hz, 1H); IR (neat) ν = 1682; MS (70 eV) *m*/*z* 148 [M$^+$], 133 [M$^+$ − CH_3] (100). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 79.90; H, 8.24.

Data for 1-(5-Ethyl-2-methylphenyl)-1-ethanone (7b):[19] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 1.23 (t, ^3J(H,H) = 7.6 Hz, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 2.64 (q, ^3J(H,H) = 7.6 Hz, 2H), 7.13 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.20 (br d, ^3J(H,H) = 7.6 Hz, 1H), 7.48 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 20 °C) δ = 15.62, 21.11, 28.35, 29.60, 128.75, 131.02, 132.01, 135.43, 137.74, 141.63, 202.02; IR (neat) ν = 1682; MS (70 eV) *m*/*z* 162 [M$^+$], 147 [M$^+$ − CH_3] (100). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.58; H, 8.74.

Data for 1-(2-Methyl-5-propylphenyl)-1-ethanone (7c):[19] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 0.93 (t, ^3J(H,H) = 7.3 Hz, 3H), 1.63 (m, 2H), 2.47 (s, 3H), 2.57 (s, 3H), 2.58 (t, ^3J(H,H) = 7.3 Hz, 2H), 7.13 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.18 (dd, ^3J(H,H) = 7.8, ^4J(H,H) = 1.7 Hz, 1H), 7.46 (d, ^4J(H,H) = 1.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 20 °C) δ = 13.73, 21.11, 24.56, 29.57, 37.43, 129.33, 131.59, 131.91, 135.46, 137.65, 140.06, 202.01; IR (neat) ν = 1683; MS (70 eV) *m*/*z* 176 [M$^+$], 161 [M$^+$ − CH_3] (100). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.68; H, 9.24.

Data for 1-(5-Butyl-2-methylphenyl)-1-ethanone (7d): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 0.94 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.38 (m, 4H), 1.61 (m, 2H), 2.49 (s, 3H), 2.58 (s, 3H), 2.62 (t, ^3J(H,H) = 7.5 Hz, 2H), 7.14 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.20 (dd, ^3J(H,H) = 7.8, ^4J(H,H) = 1.8 Hz, 1H), 7.49 (d, ^4J(H,H) = 1.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C) δ = 14.42, 21.61, 22.80, 30.07, 34.13, 35.59, 129.79, 132.06, 132.41, 135.90, 138.14, 140.77, 202.49; IR (neat) ν = 1684; MS (70 eV) *m*/*z* 190 [M$^+$], 175 [M$^+$ − CH_3] (100). Anal. Calcd for $C_{13}H_{18}O$: C, 82.05; H, 9.53. Found: C, 81.94; H, 9.64.

Data for 1-(2-Methyl-5-pentylphenyl)-1-ethanone (7e): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 0.88 (br t, ^3J(H,H) = 7.0 Hz, 3H), 1.31 (m, 4H), 1.60 (m, 2H), 2.48 (s, 3H), 2.56 (s, 3H), 2.59 (br t, ^3J(H,H) = 7.6 Hz, 2H), 7.12 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.18 (dd, ^3J(H,H) = 7.8, ^4J(H,H) = 1.7 Hz, 1H), 7.45 (d, ^4J(H,H) = 1.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C) δ = 14.53, 21.64, 23.03, 30.09, 31.68, 31.93, 35.87, 129.79, 132.06, 132.42, 135.92, 138.12, 140.81, 202.50; IR (neat) ν = 1688; MS (70 eV) *m*/*z* 204 [M$^+$], 189 [M$^+$ − CH_3] (100). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.86. Found: C, 82.42; H, 9.94.

Data for 1-(5-isopropyl-2-methylphenyl)-1-ethanone (7f):[19] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 1.25 (d, ^3J(H,H) = 7.0 Hz, 6H), 2.47 (s, 3H), 2.57 (s, 3H), 2.91 (m, 1H), 7.15 (d, ^3J(H,H) = 7.9 Hz, 1H), 7.24(dd, ^3J(H,H) = 7.9, ^4J(H,H) = 1.8 Hz, 1H) 7.50 (d, ^4J(H,H) = 1.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 20 °C) δ = 21.10, 23.98 (×2), 29.63, 33.68, 127.35, 129.51, 132.01, 135.55, 137.79, 146.31, 202.10; IR (neat) ν = 1685; MS (70 eV) *m*/*z* 176 [M$^+$], 161 [M$^+$ − CH_3] (100), 133 [M$^+$ − CH_3CO]. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.90; H, 9.24.

(16) Ballini, R.; Bosica, G. *J. Chem. Res., Synop.* **1993**, 371.
(17) Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497−1501.
(18) Dorofeenko, G. N.; Polishchuk, L. V. *Zh. Obshch. Khim.* **1962**, *32*, 364−367; *Chem. Abstr.* **1963**, *58*, 2397d.
(19) Taylor, E. P.; Watts, G. E. *J. Chem. Soc.* **1952**, 1123−1127.

Data for 1-[4-Methyl-1,1′-biphenyl]-3-ylethanone (7g): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 2.55 (s, 3H), 2.62 (s, 3H), 7.30 (d, ^3J(H,H) = 8.0 Hz, 1H), 7.37 (m, 1H), 7.45 (br t, ^3J(H,H) = 7.7 Hz, 2H), 7.58 (m, 3H), 7.87 (d, ^4J(H,H) = 2.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 20 °C) δ = 21.21, 29.67, 126.99 (×2), 127.56, 127.98, 128.92 (×2), 128.99, 130.02, 132.53, 137.25, 138.18, 140.21, 201.79; IR (neat) ν = 1691; MS (70 eV) m/z 210 [M^+], 195 [$M^+ - CH_3$] (100), 167 [$M^+ - CH_3CO$]. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.80; H, 6.64.

Data for 1-(2-Ethyl-5-methylphenyl)-1-propanone (7h): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ = 1.17 (t, ^3J(H,H) = 7.4 Hz, 6H), 2.33 (s, 3H), 2.74 (q, ^3J(H,H) = 7.4 Hz, 2H), 2.87 (q, ^3J(H,H) = 7.4 Hz, 2H), 7.14 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.18 (br d, ^3J(H,H) = 7.8 Hz, 1H), 7.31 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 20 °C) δ = 8.40, 16.15, 20.93, 26.49, 35.27, 128.34, 130.15, 131.62, 135.05, 138.52, 140.44, 205.24; IR (neat) ν = 1684; MS (70 eV) m/z 176 [M^+], 147 [$M^+ - C_2H_5$] (100). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.66; H, 9.24.

Acknowledgment. This research was carried out in the framework of the National Project "Stereoselezione in Sintesi Organica: Metodologie ed Applicazioni" supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and by the University of Camerino.

JO0006324