Pergamon

Tetrahedron Letters 40 (1999) 1157–1160

TETRAHEDRON
LETTERS

Masked Acylation of *m*-Dinitrobenzene and Derivatives with Nitroalkanes under Basic Conditions: Nitromethylation and α-(Hydroxyimino)alkylation

Takehiko Kawakami, Hitomi Suzuki*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8224, Japan

Received 21 October 1998; revised 24 November 1998; accepted 27 November 1998

Abstract

m-Dinitrobenzene and derivatives react with nitromethane or some other primary nitroalkanes in the presence of lithium *tert*-butoxide in 1,3-dimethyl-2-imidazolizinone (DMI) at room temperature, giving the corresponding 4-nitromethyl and 4-[1-(hydroxyimino)alkyl] derivatives, respectively, in moderate yields. These products are smoothly converted to the corresponding carbonyl compounds by oxidative Nef reaction using ozonized oxygen. © 1999 Elsevier Science Ltd. All rights reserved.

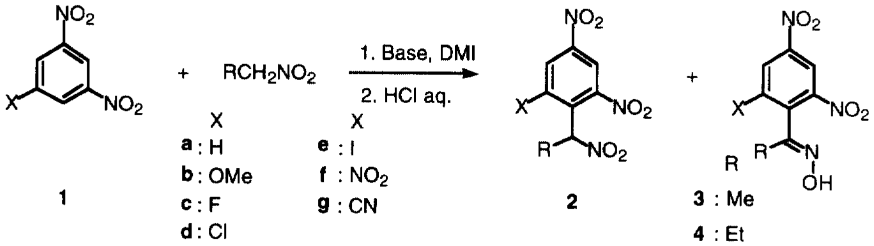
Keywords: Acylation; Carbanions; Nitro compounds; Substitution.

Base-catalyzed aldol-type condensation and Michael-type addition of nitroalkanes have been widely employed as convenient tools for the functionalization of carbonyl and activated olefinic compounds. However, the nitronate-based nucleophilic substitution has scarcely been employed for the functionalization of aromatic nuclei due to low reactivity of the nitronate anion as well as extensive competing side reactions. [1] A major breakthrough in this aspect of aromatic chemistry has been achieved by Makosza and coworkers in mid 1980's, [2,3] who treated 1-nitronaphthalene and three nitroquinolines with nitromethane in the presence of sodium hydroxide in dimethyl sulfoxide (DMSO) at room temperature, obtaining the corresponding nitromethylation products in 30-55% yield. The nitromethyl group is always introduced at position next to the nitro group. However, this attractive nitroalkylation has been described to fail with monocyclic nitroarenes. [2]

In this paper, we wish to report that *m*-dinitrobenzene and derivatives **1** react with nitromethane and some other primary nitroalkanes in the presence of lithium *tert*-butoxide in 1,3-dimethyl-2-imidazolizinone (DMI) at room temperature, giving the corresponding 4-nitromethyl or 4-[1-(hydroxyimino)alkyl] derivatives **2/3,4** in fair to moderate yield. The

PII: S0040-4039(98)02552-0

reaction proceeds quite reluctantly in DMF and DMSO to give the product in low yield, while it does not take place in THF. The nitroalkylation is highly regio- and chemoselective, only the hydrogen atom at 4-position being preferentially substituted. When located at 5-position, such good nucleofugal substituents as halogen atom and nitro group still remain intact. Under these conditions, nitrobenzene and 1-nitronaphthalene do not produce the expected nitroalkylation products. The use of lithium *tert*-butoxide requires longer reaction time as compared with other bases such as potassium *tert*-butoxide, sodium hydride and lithium hydride, but the reaction is cleaner probably due to the intrinsic nature of this base as a weak nucleophile and a strong base. When potassium *tert*-butoxide is used, the reaction is accompanied by small amounts of 2,4-dinitrophenol and much tarry substances. Sodium hydride is such stronger a base that it causes extensive decomposition of the substrates during the reaction, resulting in significant decrease of the product yields. Similarly, the use of lithium hydride leads to a considerable decrease in the yield of the expected product. Using lithium *tert*-butoxide, however, the unchanged substrates can be recovered and cycled for reuse.



Scheme 1

Similar reaction of 5-substituted 1,3-dinitrobenzenes **1b-f** with nitromethane gives the corresponding nitromethylation products **2b-f** in 24-60% yields. These yields are comparable with those from the nitromethylation of *m*-dinitrobenzene **1a**, irrespective of the electronic nature of the substituent group present at 5-position. The hydrogen atom at 4-position is always displaced with similar ease by a nitronate anion.

When *m*-dinitrobenzene **1a** is reacted with nitroethane or 1-nitropropane under similar conditions, oxime derivatives **3a** and **4a** of the corresponding acylophenones are obtained in 40 and 36 % yields, respectively. In contrast, attempted reactions of **1a** with arylnitromethanes and secondary nitroalkanes fail to give the expected products, probably due to the lower reactivity as well as bulkiness of the resulting nitronate anions. In this regard, the present nitroalkylation may be complementary to the Kornblum's nitroalkylation, where the activated nitroarenes react with lithium salt of secondary nitroalkanes in dipolar aprotic solvent, giving the products in which the nitro group is displaced by an α-branched 1-nitroalkyl group. [4,5]

The formation of aldehydes and ketones from alkaline salts of primary and secondary nitroalkanes has been known as the Nef reaction. [6] Thus, Makosza and coworkers converted their nitromethylation products to the corresponding aldehydes in good yield via

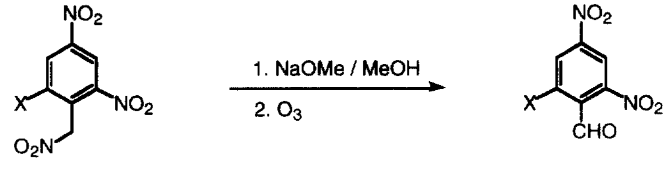
Table 1. Base-assisted reaction of *m*-dinitrobenzenes and derivatives **1a-g** with nitroalkanes^{a}

Nitroarene		Nitroalkane	Base	Time	Yield (%)^{b}		m.p.	^{1}H NMR
	X	R	(equiv)	(h)	**2**	**3/4**	(°C)	(CH$_2$NO$_2$, δ)
1a	H	H	LiH (4.0)	24	20 (38)^{c}	-	141	5.96
			LiH (8.0)	24	23	-		
			LiO^{t}Bu (4.0)	24	39 (66)^{c}	-		
				216	62	-		
			LiO^{t}Bu (8.0)	6	26 (46)^{c}	-		
				24	44	-		
1b	OMe	H	LiO^{t}Bu (4.0)	24	37 (62)^{c}	-	oil	5.94
				72	60	-		
1c	F	H	LiO^{t}Bu (4.0)	24	24	-	oil	5.99
1d	Cl	H	LiO^{t}Bu (4.0)	24	53	-	oil	5.99
1e	I	H	LiO^{t}Bu (4.0)	24	36	-	oil	6.09
1f	NO$_2$	H	LiO^{t}Bu (4.0)	24	42	-	oil	6.13
1g	CN	H	LiO^{t}Bu (4.0)	24	trace^{d}	-	-	
1a	H	Me	LiO^{t}Bu (8.0)	24	-	17 (46)^{c}	118	
				216	-	40		
		Et	LiO^{t}Bu (8.0)	24	-	15 (40)^{c}	106	
				216	-	36		

[a] All reactions were carried out using substrate (0.30 g), nitroalkane (2.0 equiv) and DMI (30 mL) at room temperature. [b] Yields refer to the isolated compounds. [c] Numerals in parentheses refer to the yields based on unrecovered substrates. [d] Cyano group is not tolerable under the conditions employed.

the oxidative Nef reaction, using potassium permanganate in a borate buffer. [2] However, this methodology fails to work with substituted arylnitromethanes **2b-g** under the reported conditions. When the reaction is attempted under forced conditions, extensive decomposition occurs and little or no carbonyl compounds are obtained. This failure is most likely to arise from steric inhibition of the Nef reaction by the substituent groups at 3 and 5-positions. The transformation of arylnitromethanes **2a-f** into the corresponding substituted benzaldehydes **5a-f** is successfully performed by the oxidative Nef reaction using ozonized oxygen. [7] The results obtained are listed in Table 2. The present methodology may find use for the preparation of some substituted arylnitromethanes and aromatic aldehydes, which are otherwise laborious to obtain.

Preparation of Arylnitromethanes 2a-f. Typical Procedure: *tert*-Butanol (0.75 mL) is added to a stirred suspension of LiH (57 mg) in DMI (30 mL). To the resulting solution of lithium *tert*-butoxide is added nitromethane (0.20 mL) followed by *m*-dinitrobenzene **1a** (0.30 g) at room temperature. After stirring for 24 h at the same temperature, the reaction



2

5

Table 2. Substituted benzaldehydes **5a-f** obtained[a]

Substrate	m.p. (°C)	Yield (%)	Substrate	m.p. (°C)	Yield (%)
5a	72 (lit., [8] 69-71)	82	**5d**	89	80
5b	94	86	**5e**	102	66
5c	76	78	**5f**	119 (lit., [9] 119)	70

[a] All new compounds gave satisfactory elementary analyses: C ± 0.30 %, H ± 0.12 %, N ± 0.35 %.

mixture is poured into 1 N HCl (100 mL) and the organic phase is extracted with benzene (3 x 30 mL). The solvent is removed under reduced pressure to leave a solid residue, which is chromatographed on silica gel using hexane-ethyl acetate as the solvent to give 2,4-dinitrophenylnitromethane **2a** as yellow crystals (0.16 g, 39 %), m.p. 141-142 °C, (Anal. Calcd for $C_7H_5N_3O_6$: C, 37.02; H, 2.22; N, 18.50. Found: C, 37.30; H, 2.23; N, 18.23). Unchanged **1a** (0.12 g, 41 %) is recovered.

Preparation of Substituted Benzaldehydes 5a-f. Typical Procedure. To a solution of arylnitromethane **2a** (0.25 g, 0.96 mmol) in methanol (50 mL) is added sodium methoxide (60 mg, 1.0 mmol) in one portion. The resulting mixture is stirred at room temperature, while ozonized oxygen is slowly passed into the solution. After 1 h the mixture is diluted with water (150 mL) and the organic phase is extracted with dichloromethane (3 x 30 mL). The combined extracts are evaporated and the residue is chromatographed on silica gel using hexane-ethyl acetate as the eluent to give 2,4-dinitrobenzaldehyde **5a** as yellow crystals (0.17 g, 80 %), m.p. 71-72 °C (lit. [8] 69-71 °C).

References

[1] (a) Miller J. "Aromatic Nucleophilic Substitution"' Elsevier. Amsterdam, 1968. (b) Terrier F. "Nucleophilic Aromatic Displacement. The Influence of the Nitro Group" VCH Publishers, Inc. New York, 1991. (c) Chupakhin ON, Charushin VN, van der Plas HC. "Nucleophilic Aromatic Substitution of Hydrogen" Acad. Press, San Diego, 1994.

[2] Danikiewicz W, Makosza M. Tetrahedron Lett. 1985; **26**: 3599 - 3600.

[3] Rykowski A, Makosza M. Tetrahedron Lett. 1984; **25**:4795 - 4796.

[4] Kornblum N, Cheng L, Kerber RC, Kestner MM, Newton BN, Pinnick HW, Smith RG, Wade PA. J. Org. Chem. 1976; **41**:1560-1564.

[5] Norris RK, Randles D. Aust. J. Chem. 1979; **32**:2413-2422.

[6] Pinnick HW. Org. React. 1989; **38**: 655 - 792.

[7] McMurry JE, Melton J, Padgett H. J. Org. Chem. 1974; **39**: 259 - 260.

[8] Bennett GM, Bell EV. Org. Synth. 1943; Coll. Vol. 2 **2**: 223 – 225.

[9] Sachs F, Kempf R. Ber. Dtsch. Chem. Ges. 1902; **35**: 1224-1240.