An Improved Procedure for the Preparation of β-Nitroethylamines

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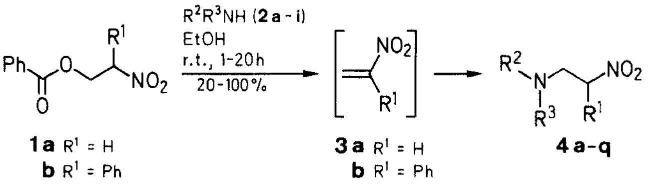
Nitroethylene and α-nitrostyrene, generated in situ from 2-benzoyloxy-1-nitroethane and 2-benzoyloxy-1-nitro-1-phenylethane respectively, reacted with aliphatic amines to give the corresponding Michael adducts in near quantitative yield.

In connection with our research on biologically active compounds, a practical route for the addition of nitrogen-centered nucleophiles to unsubstituted or α-substituted nitroalkenes was needed. Despite a pertinent accumulation of nitroolefin chemistry,[1] the literature contains scattered reports concerning the addition of amines to conjugated nitroalkenes, a reaction first studied by Wieland[2] and recently investigated in details by Ranganathan et al.,[3] who demonstrated that the reaction is limited to bases having pk_a in the range of 2–8 (i.e.: aromatic, aliphatic amines carrying an α-electron-withdrawing group), failing with nitrogen bases of higher pk_a, owing to the propensity of nitroalkenes to undergo base-catalyzed anionic polymerization.

In this paper we wish to report a simple and practical method for the addition of aliphatic amines ($pk_a > 8$) to both nitroethylene **3a** or α-nitrostyrene **3b**, usually obtained by dehydration of the corresponding nitroalcohols using various reagents, including dicyclohexylcarbodiimide,[4] pivaloyl chloride,[5] methanesulfonyl chloride[6] or phthalic anhydride.[7]

We have found it more convenient to generate both **3a** and **3b** in situ from the corresponding accessible precursors **1a,b**[8] by treating them with the appropriate nitrogen base **2a–i** at room temperature in ethanolic solution. (Scheme) This modification[9] allowed to obtain a practically quantitative yield of the Michael adducts **4a–o** through benzoic acid assisted neutralization of the nitronate anion intermediate, which prevents the base-catalyzed polymerization of the very reactive nitroalkenes. Thus, primary amines such as benzylamine and cyclohexylamine react with both **1a** and **1b** to give different ratio of mono- and bisadducts (Table 1 and 2). An obvious device to obtain only monoadducts is represented by the utilization of a secondary amine bearing a substituent removable at a later stage (i.e., the adduct **4o** from N-benzyl-β-alanine methyl ester). Secondary amines, i.e., piperidine and dibutylamine undergo easy addition to both **3a** and **3b**, while those carrying sterically bulky substituents on nitrogen such as dicyclohexylamine and diisopropylamine failed to undergo addition, catalyzing only polymerization. The low basicity of aromatic amines, while allowed easy Michael addition to nitroalkenes following Ranganathan' protocol,[3] precluded their reaction under these conditions. On the other hand our method made the formation of two interesting adducts possible, namely N-(2-nitroethyl)- and N-(2-nitro-2-phenylethyl)imidazole, the addition products of **3a** and



2	R^2	R^3	2	R^2	R^3
a	H	Bn	f	Bn	$(CH_2)_2CO_2Me$
b	H	c-C_6H_{11}	g	c-C_6H_{11}	c-C_6H_{11}
c	$-(CH_2)_5-$		h	i-Pr	i-Pr
d	$-CH{=}N{-}CH{=}N-$		i	H	Ph
e	Bu	Bu			

Scheme

Table 1. β-Nitroethylamine 4 Prepared

Starting Materials[a]	Product[a]	Reaction Time (h)	R^1	R^2	R^3	Ratio of mono/bisadduct
1a + 2a	**4a**	8	H	H	Bn	1 : 1
	4b		H	$CH_2CH_2NO_2$	Bn	
1b + 2a	**4c**	20	Ph	H	Bn	7 : 3
	4d		Ph	$CH_2CHPhNO_2$	Bn	
1a + 2b	**4e**	1	H	H	c-C_6H_{11}	1 : 1
	4f		H	$CH_2CH_2NO_2$	c-C_6H_{11}	
1b + 2b	**4g**	2	Ph	H	c-C_6H_{11}	8 : 2
	4h		Ph	$CH_2CHPhNO_2$	c-C_6H_{11}	
1a + 2c	**4i**	7	H	$-(CH_2)_5-$		
1b + 2c	**4j**	1.5	Ph	$-(CH_2)_5-$		
1a + 2d	**4k**	1.5	H	$-CH{=}N{-}CH{=}CH-$		
1b + 2d	**4l**	5	Ph	$-CH{=}N{-}CH{=}CH-$		
1a + 2e	**4m**	0.5	H	Bu	Bu	
1b + 2e	**4n**	3	Ph	Bu	Bu	
1a + 2f	**4o**	3	H	Bn	$CH_2CH_2CO_2Me$	

[a] The starting materials **1a + 2g**, **1b + 2g**, **1a + 2h** and **1b + 2h**, respectively, yielded only polymer products; **1a + 2i** gave no reaction.

Table 2. Physical and Spectral Data of β-Nitroethylamines **4**

Product[a]	Yield (%)	Molecular Formula[b]	IR (film) ν (cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, J (Hz)
4a	48	$C_9H_{12}N_2O_2$ (180.2)	3400, 1560	1.80 (s, 1H), 3.20 (t, 2H, J = 7), 3.80 (s, 2H), 4.50 (t, 2H, J = 7), 7.30 (m, 5H)
4b	49	$C_{11}H_{15}N_3O_4$ (253.25)	1560	3.20 (t, 4H, J = 7), 3.70 (s, 2H), 4.40 (t, 4H, J = 7), 7.30 (m, 5H)
4c	70	$C_{15}H_{16}N_2O_2$ (256.3)	3400, 1560	1.70 (br s, 1H), 3.07 (dd, 1H, J = 4.4, 13.5), 3.73 (dd, 1H, J = 10, 13.5), 3.85 (s, 2H), 5.58 (dd, 1H, J = 4.4, 10), 7.30–7.50 (m, 10H)
4d	30	$C_{23}H_{23}N_3O_4$ (405.4)	1560	2.90–3.30 (m, 2H), 3.50–4.00 (m, 4H), 5.35–5.50 (m, 2H), 7.00–7.60 (m, 15H)
4e	50	$C_8H_{16}N_2O_2$ (172.2)	3400, 1550	1.00–1.40 (m, 4H), 1.60–2.00 (m, 6H), 2.50 (m, 1H), 3.20 (t, 2H, J = 7), 4.50 (t, 2H, J = 7)
4f	50	$C_{10}H_{19}N_3O_4$ (245.3)	1550	1.00–1.40 (m, 4H), 1.60–2.00 (m, 6H), 2.38 (m, 1H), 3.16 (m, 4H), 4.50 (m, 4H)
4g	80	$C_{14}H_{20}N_2O_2$ (248.3)	3400, 1550	1.00–1.90 (m, 10H), 2.00 (br s, 1H), 2.45 (m, 1H), 3.10 (dd, 1H, J = 3.5, 14), 3.70 (dd, 1H, J = 14, 8), 5.57 (dd, 1H, J = 8, 3.5), 7.30–7.50 (m, 5H)
4h	20	$C_{22}H_{27}N_3O_4$ (397.5)	1550	1.00–1.90 (m, 10H), 2.50 (m, 1H), 3.00 (m, 2H), 3.70 (m, 2H), 5.20–5.40 (m, 2H), 7.30–7.50 (m, 10H)
4i	94	$C_7H_{14}N_2O_2$ (158.2)	1550	1.40 (m, 2H), 1.60 (m, 4H), 2.45 (m, 4H), 2.98 (t, 2H, J = 7), 4.50 (t, 2H, J = 7)
4j	98	$C_{13}H_{18}N_2O_2$ (234.29)	1550	1.20–1.80 (m, 6H), 2.40 (m, 2H), 2.60 (m, 2H), 2.65 (dd, 1H, J = 3.3, 13.8), 3.56 (dd, 1H, J = 13.8, 11), 5.67 (dd, 1H, J = 3.3, 11), 7.20–7.50 (m, 5H)
4k	83	$C_5H_7N_3O_2$ (141.13)	1550	4.60 (m, 2H), 4.75 (m, 2H), 6.97 (s, 1H), 7.10 (s, 1H), 7.60 (s, 1H)
4l	97	$C_{11}H_{11}N_3O_2$ (217.22)	1550	4.45 (dd, 1H, J = 4, 16), 5.05 (dd, 1H, J = 9.6, 16), 5.75 (dd, 1H, J = 9.6, 4), 6.90 (s, 1H), 7.05 (s, 1H), 7.30 (s, 1H), 7.30–7.50 (m, 5H)
4m	97	$C_{10}H_{22}N_2O_2$ (202.29)	1550	0.90 (t, 6H, J = 7.5), 1.20–1.45 (m, 8H), 2.40 (t, 4H, J = 7.5), 3.05 (t, 2H, J = 7), 4.40 (t, 2H, J = 7)
4n	100	$C_{16}H_{26}N_2O_2$ (278.38)	1550	0.90 (t, 6H, J = 7.5), 1.20–1.50 (m, 8H), 2.40–2.65 (m, 4H), 2.75 (dd, 1H, J = 14, 3), 3.65 (dd, 1H, J = 14, 12), 5.60 (dd, 1H, J = 3, 12), 7.30–7.50 (m, 5H)
4o	99	$C_{13}H_{18}N_2O_4$ (266.29)	1735, 1550	2.46 (t, 2H, J = 6.8), 2.85 (t, 2H, J = 6.8), 3.10 (t, 2H, J = 6), 3.64 (s, 2H), 3.66 (s, 3H), 4.38 (t, 2H, J = 6), 7.28 (m, 5H)

[a] All compounds were isolated as homogeneous oils after flash chromatography (eluents see General Procedure).

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.29, N ±0.28.

[c] Recorded on Bruker AC 200 spectrometer.

3b, respectively, with imidazole which, in spite of favorable pK_a gave only polymers by direct nitroethylation procedure.[3]

In conclusion, we have developed a practical procedure for the addition of aliphatic amines and heterocyclic bases to reactive nitroalkenes, conveniently generated in situ from accessible precursors, which complements well the existing methods.

β-Nitroethylamines 4; General Procedure:

A mixture of the nitro derivative **1a** or **1b** (3 mmol) and the appropriate amine **2** (3 mmol) in absolute EtOH (20 mL) is stirred at r.t. until complete disappearance of the starting materials (the reaction progress is monitored by TLC). The solvent is removed under reduced pressure, the residue dissolved in Et_2O (25 mL) and washed with sat. aq $NaHCO_3$ (20 mL). After drying ($MgSO_4$), the solvent is evaporated under vacuum to leave the adducts **4a–q**, which are purified by flash chromatography on silica gel [eluent Et_2O/light petroleum ether (bp 40–60 °C) ; [4:1 (for **4a,b,e,f,i,k,m**), 1:1 (for **4c,d,g,h,j,l**), 2:1 (for **4o**).]. These nitroamines should be kept in the refrigerator, since we found them to be unstable to prolonged standing at r.t.

Thanks are due to Ministero dell'Universitá e della Ricerca Scientifica e Tecnologica (60 %) for financial support.

Received: 2 November 1990; revised: 21 January 1991

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