Pergamon

Tetrahedron Letters 43 (2002) 5233–5235

TETRAHEDRON
LETTERS

Unprecedented, selective Nef reaction of secondary nitroalkanes promoted by DBU under basic homogeneous conditions

Roberto Ballini,* Giovanna Bosica, Dennis Fiorini and Marino Petrini

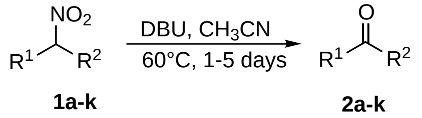
Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, I-62032 Camerino, Italy

Received 31 May 2002; accepted 4 June 2002

Abstract—Secondary nitrocompounds can be converted into the corresponding ketones under basic conditions using DBU in acetonitrile. Primary nitroalkanes are unaffected by these conditions. © 2002 Elsevier Science Ltd. All rights reserved.

Nitro compounds are very powerful synthetic tools because they facilitate the carbon–carbon bond-forming processes and, moreover, they can be easily converted into many other useful functionalities.[1] The conversion of primary or secondary nitroalkanes into aldehydes or ketones is normally accomplished by the Nef reaction, which is one of the most important transformations of the nitro compounds.

The original Nef reaction involves the formation of an alkaline nitronate, followed by a quick solvolysis in aqueous or alcoholic strong acidic solution.[2] This procedure clearly requires rather harsh conditions that are often incompatible with many acid-sensitive functional groups that could be present in the molecular framework. For this reason a number of synthetic methods have been devised in order to perform cleavage of the carbon–nitrogen bond in nitroalkanes under mild and selective conditions.[3] Hydrolysis of the C=N bond of nitronates can be replaced by an oxidative cleavage that can be carried out with several reagents including $KMnO_4$,[4] *m*CPBA,[5] MoO_5–pyridine–HMPA complex,[6] ceric ammonium nitrate,[7] ozone,[8] sodium chlorite,[9] sodium nitrite in DMSO[10] and dimethyldioxirane (DMD).[11] On the other hand, reduction of the nitro group to the corresponding oxime or imine followed by hydrolysis to the parent carbonyl derivative allows an alternative route for this transformation. The utilization of titanium trichloride as reducing agent[12] has been followed by the introduction of other reagents such as vanadium(II) chloride,[13] chromium(II) chloride[14] and the combined use of tributylphosphine–diphenyldisulfide.[15] However, the use of the above conditions is not of general utility since they are often incompatible with polyfunctional substrates and none of these are able to convert selectively a secondary nitro group in the presence of a primary one. In fact, to the best of our knowledge, although some oxidative methods[16] show selectivity towards the transformation of primary nitro compounds, these procedures are seldom utilizable in synthetic processes since the primary nitro group is often partially converted into aldehydes,[16a] halonitroalkanes,[5] or into an intractable mixture of products.[16b] Direct cleavage of the nitronate anion under basic conditions is a rather uncommon process that has been observed on dry activated silica gel[17] or when proton transfer is facilitated by a neighboring group participation.[18] 1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU), a tertiary amidine base, has been largely used to promote the addition of nitroalkanes to electrophilic substrates for the formation of both carbon–carbon single bonds[19] and carbon–carbon double bonds.[20] Now, we have found an unprecedent behaviour of DBU as a new reagent for the regio- and chemoselective conversion of secondary nitro compounds into ketones, under homogeneous basic conditions. Thus, treating 1 equiv. of the nitroalkane with 2 equiv. of DBU in CH_3CN, and heating at 60°C for 1–5 days, the secondary nitro compounds **1a**–**k** (Eq. (1)) are converted into the corresponding ketones **2a**–**k** in 54–80% yields (Table 1), while the primary nitroalkanes **1l**–**n** are unreacted.[21]



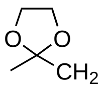
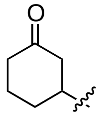
(1)

Keywords: nitro compounds; ketones.

* Corresponding author. Tel.: +39 0737 402270; fax: +39 0737 402297; e-mail: roberto.ballini@unicam.it

PII: S0040-4039(02)01039-0

Table 1. Conversion of secondary nitroalkanes **1a**–**k** to ketones **2a**–**k**

Entry	Nitrocompound **1**		Time (days)	Yield[a] (%)
	R^1	R^2		
a	$Ph(CH_2)_3$	$CH_3(CH_2)_2$	4	60
b	$MeOCO(CH_2)_2$	$MeOCO(CH_2)_4$	2	65
c		$MeOCO(CH_2)_2$	4	80
d	$MeOCO(CH_2)_4$	$CH_3CO(CH_2)_2$	5	61
e	CH_3	$Me(CH_2)_2CO$-$(CH_2)_2$	1	58
f	CH_3	$C_2H_5CO(CH_2)_2$	4	55
g	$CH_3(CH_2)_3$	$C_2H_5CO(CH_2)_2$	5	59
h		CH_3	5	54
i	$CH_3CO(CH_2)_2$	$C_2H_5CO(CH_2)_2$	1	55
j	$MeOCO(CH_2)_2$	$MeOCO(CH_2)_2$	5	65
k	$HOCH_2(CH_2)_4$	$MeOCO(CH_2)_2$	2	56
l	$CH_3(CH_2)_4$	H	–	–
m	$MeOCO(CH_2)_3$	H	–	–
n	$CH_3(CH_2)_8$	H	–	–

[a] Yields of pure, isolated products.

We also tried THF as solvent, but CH_3CN gives better yields in shorter reaction times. We also investigated the selective conversion of a secondary nitroalkane **1a** in the presence of the primary nitroalkane **1n**; after 4 days the GC analysis indicated a complete conversion of **1a** to **2a** in 58% yield, while **1n** was recovered unchanged from the reaction mixture in 92% yield.

Although DBU is the most effective reagent tested for this conversion, other bases of similar structure are able to carry out the same transformation to some extent. Data reported in Table 2 refer to the transformation of nitroalkane **1a** into ketone **2a** and show that 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) has an efficiency similar to that observed with DBU (entry 2). Guanidines display a variable behaviour depending on their structural features; *N*,*N*,*N*,*N*-tetramethylguanidine (TMG) gives unsatisfactory results (entry 4), while a bicyclic guanidine such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) possesses a good activity towards the conversion of **1a** into **2a** (entry 3). However, the efficiency of TBD seems to be strongly affected by the nature of nitroalkane employed, since with other substrates the yields of the process are lower compared with those obtained with DBU.

Triphenylphosphine, tributylphosphine as well as 4-dimethylaminipyridine (DMAP) are unable to react efficiently with the secondary nitroalkanes tested as reported in Table 2 (entries 5–7). It is generally understood that a certain acidity level is displayed by nitroalkanes in water or other hydroxylic solvents (pK_a $MeNO_2 = 10.2$), however, the acidity is considerably lower when these derivatives are used in other solvents as acetonitrile, THF or benzene in which proton transfer can be suppressed. Davis and co-workers[22] have demonstrated that DBU in acetonitrile is not able to efficiently convert nitroethane into the corresponding nitronate since only a broadening of the α-protons signals in ^1H NMR is observed. The situation could be different when secondary nitroalkanes are used as substrates since they are slightly more acidic than the primary ones. It is therefore possible that DBU is able to produce a complex **3**, as depicted in Scheme 1, that behaves similarly to a protonated nitronic acid intermediate in the classical Nef reaction. In the absence of a significant amount of water, it is conceivable that, similarly to what was observed with nitrones[23] that are structurally related with nitronic acids, an equilibrium occurs between the complex **3**, the oxaziridine **4** and the hydroxynitroso derivative **5**. The last intermediate would eliminate hyponitrous acid affording the carbonyl derivative as the final product.

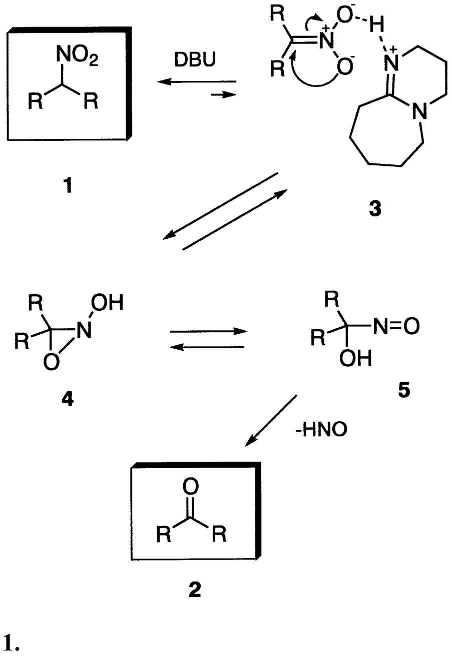
Table 2. Conversion of nitroalkane **1a** to ketone **2a** using different bases

Entry	Base[a]	Time (days)	Yield[b] % (conversion %)[c]
1	DBU	4	60 (100)
2	DBN	3	50 (80)
3	TBD	1	55 (96)
4	TMG	3	25 (33)[c]
5	Bu_3P	3	5 (8)[c]
6	Ph_3P	3	7 (10)[c]
7	DMAP	3	8 (12)[c]

[a] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN: 1,5-diazabicyclo-[4.3.0]non-5-ene; TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG: tetramethylguanidine; DMAP: 4-dimethylaminopyridine.

[b] Yields of pure, isolated products.

[c] Yields evaluated by GC analysis using an internal standard.



Scheme 1.

In conclusion a one-step conversion of secondary nitrocompounds into the corresponding carbonyl derivatives can be carried out in good yield using DBU in acetonitrile. Many functionalities that are difficult to preserve under acidic (i.e. ketal), oxidative (i.e. hydroxyl), or reductive (i.e. carbonyl) conditions that are generally employed for the Nef reaction are unaffected by this process. Moreover, the efficient chemoselective conversion of a secondary nitro group in the presence of a primary one is now possible.

Acknowledgements

This work was carried out in the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by MIUR (Ministero dell'Istruzione dell'Università e della Ricerca), Italy and by the University of Camerino.

References

1. (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1–17; (b) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833–847; (c) Ballini, R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1997; Vol. 19, pp. 117–184; (d) Ballini, R. *Synlett* **1999**, 1009–1018; (e) Ono, N. In *The Nitro Group in Organic Synthesis*; John Wiley: New York, 2001; (f) *Nitro Compounds, Recent Advances in Synthesis and Chemistry*, Feuer, H.; Nielsen, A. T., Eds.; VCH: Weinheim, 1990; (g) Torssell, K. B. G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988.
2. (a) Nef, J. V. *Ann. Chem.* **1899**, *308*, 264–333; (b) Noland, W. E. *Chem. Rev.* **1955**, *55*, 137–155.
3. Pinnick, H. W. *Org. React.* **1990**, *38*, 655–792.
4. (a) Freeman, F.; Lin, D. K. *J. Org. Chem.* **1971**, *36*, 1335–1338; (b) Shechter, H.; Williams, F. T. *J. Org. Chem.* **1962**, *27*, 3699–3701; (c) Kornblum, N.; Erickson, A. S.; Kelly, W. J.; Henggeler, B. *J. Org. Chem.* **1982**, *47*, 4534–4538; (d) Steliou, K.; Poupart, M. A. *J. Org. Chem.* **1985**, *50*, 4971–4973; (e) Saville-Stones, E. A.; Liddell, S. D. *Synlett* **1991**, 591–592.
5. Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 5361–5364.
6. Galobardes, M. R.; Pinnick, H. W. *Tetrahedron Lett.* **1981**, *22*, 5235–5238.
7. Olah, G. A.; Gupta, B. G. B. *Synthesis* **1980**, 44–45.
8. McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259–260.
9. Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1989**, *30*, 5329–5332.
10. (a) Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38*, 1418–1420; (b) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234–235.
11. Adam, W.; Makosza, M. J.; Saha-Möller, C. R.; Zhao, C.-G. *Synlett* **1998**, 1335–1336.
12. McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367–4373.
13. Kirchhoff, R. *Tetrahedron Lett.* **1976**, 2533–2534.
14. Hanson, S. P. *Synthesis* **1974**, 1–8.
15. Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2243–2252.
16. (a) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Tetrahedron Lett.* **1983**, *24*, 5227–5230; (b) Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 207–209.
17. Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3861–3862.
18. Wilson, H.; Lewis, E. S. *J. Am. Chem. Soc.* **1972**, *94*, 2283–2285.
19. (a) Ono, N.; Miyake, H.; Kamimura, A.; Tsukui, N.; Kaji, A. *Tetrahedron Lett.* **1982**, *23*, 2957–2960; (b) Ono, N.; Kamimura, A.; Kaji, A. *Synthesis* **1984**, 226–227; (c) Bunce, R. A.; Drumright, R. E. *Org. Prep. Proc. Int.* **1987**, *19*, 471–475; (d) Andruszkiewicz, R.; Silverman, R.-B. *Synthesis* **1989**, 953–955; (e) Backvall, J.-E.; Juntunen, S. K. *Tetrahedron Lett.* **1992**, *33*, 131–134; (f) Kahori, K.; Hashimoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3088–3093; (g) Sosnicki, J. G.; Liebscher, J. *Synlett* **1996**, 1117–1118.
20. (a) Ballini, R.; Rinaldi, A. *Tetrahedron Lett.* **1994**, *35*, 9247–9250; (b) Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213–4222; (c) Ballini, R.; Bosica, G.; Fiorini, D.; Gil, M. V.; Petrini, M. *Org. Lett.* **2001**, *3*, 1265–1267.
21. **General procedure**. The nitroalkane **1** (1 mmol) was dissolved in acetonitrile (10 mL) and then DBU (2 mmol) was added at room temperature. The solution was stirred at 60°C for the appropriate time (see Table 1) and then the solvent was removed under reduced pressure. The oily residue was purified by column chromatography (hexane–ethyl acetate, 8:2).
22. Boyle, P. H.; Convery, M. A.; Davis, A. P.; Hosken, G. D.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1992**, 239–242.
23. Breuer, E. In *Nitrones, Nitronates and Nitroxides*; Patai, S.; Rappoport, Z., Eds.; John Wiley: Chichester, 1989; p. 161.