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# Chemoselective $S_N2'$ reaction of nitroalkanes to dialkyl 2-(bromomethyl)fumarates under cetyltrimethylammonium hydroxide (CTAOH) catalysis

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Dedicated to our mentor, Prof. Goffredo Rosini, on the occasion of his 70th birthday

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ABSTRACT

The chemoselective $S_N2'$ reaction of a variety of primary nitroalkanes to dialkyl 2-(bromomethyl)fumarates can be efficiently performed under cetyltrimethylammonium hydroxide (CTAOH) catalysis. The α,β-unsaturated esters were obtained in satisfactory to good yields with the complete retention of the nitro group.

Nitroalkanes are powerful source of stabilized carbanions prone to give the generation of new C,C bond mainly by the conjugate addition to electron-poor alkenes (Michael reaction)[1] or by the nitroaldol (Henry) reaction with carbonyl derivatives.[2] In this context, the nucleophilic substitution reactions of halides with nitroalkanes are less exploited because it works well just with particular substrates in which the electrophilic carbon is activated by an electron-withdrawing group.[3] Few years ago, Amri and coworkers reported[4] an interesting reaction of simple primary nitroalkanes (nitroethane and 1-nitropropane, Scheme 1) **1** with dialkyl 2-(bromomethyl)fumarate **2**,[5] under NaOH catalysis, with the simultaneous elimination of both bromhydric and nitrous acids (favored by the presence of an acidic hydrogen in α-position with respect to the ester in the adduct **3**) and the consequent formation of conjugated dienes **4**.

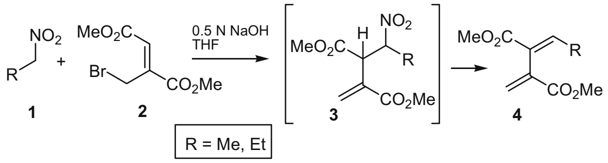
However, in spite of the great utility of the obtained dienes **4**, the elimination of the nitro group and the formation of the diene, represent an important loss in terms of further chances, from synthetic point of view, due to the possible conversion of the nitro group into a variety of other useful functionalities. Thus, a new, chemoselective catalytic procedure for the reaction of **1** to **2**, preserving the presence of the nitro group would be highly welcome.

Recently, we developed a new method for the conjugate addition of nitroalkanes to standard electrophilic alkenes under cetyltrimethylammonium hydroxide (CTAOH, 10% water solution) catalysis.[6] The procedure was very efficient and the mild reaction conditions assure high chemoselectivity of the method. Now we have found that CTAOH can be efficiently applied in the chemoselective $S_N2'$ reaction of nitroalkanes with bromomethylfumarate, with the complete retention of the nitro group.

The efficiency of CTAOH was compared with other basic catalysts and, with this purpose, we selected the reaction of 1-nitropentane **1b** with dimethyl 2-(bromomethyl)fumarate **2a** as sample reaction (Table 1).

It is evident that considering: (i) yield, (ii) reaction time, and (iii) amount of catalyst the use of CTAOH is strongly preferred.

The reaction was performed by the addition of the catalyst (0.625 mmol, 0.950 mL of CTAOH, 10% water solution) to a stirred



**Scheme 1.** One-pot synthesis of dienes via $S_N2'$ reaction.

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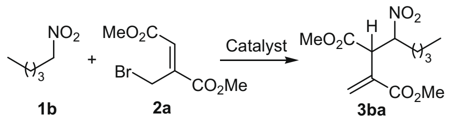
**Table 1**
Effect of a variety of catalysts for the preparation of **3a**



**1b** **2a** **3ba**

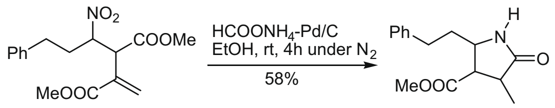
| Catalyst | Mmol of catalyst | Time (h) | Yield (%) of **3ba** |
|---|---|---|---|
| $NaCO_3$- on polymer support | 0.5 | Overnight | 44 |
| CTAOH | 0.625 | 7 | 70 |
| TBAF | 0.625 | 7 | 50 |
| $KF/Al_2O_3$[7] | 2.2 | 7 | 69 |
| DBU | 1.5 | 1[a] | 27 |
| $K_2CO_3$ | 0.7 | 18 | Traces |
| *t*-BuOK | 0.6 | 7 | Traces |

[a] Large amount of nitrous acid elimination was observed.

solution of **1b** (1.2 mmol) and **2a** (1 mmol), at 0 °C. After 5 min the reaction was allowed to stir at room temperature for the appropriate time (Table 2), and was extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under vacuum to afford the crude product **3ba** that was purified on flash chromatography (cyclohexane–EtOAc).

Then, a number of other different nitroalkanes **1** (including the secondary nitroalkane, **1m**) and dialkyl 2-(bromomethyl)fumarate **2** were chosen in order to assess the generality of our procedure. As reported in Table 2, a large variety of adducts **3** were isolated as a mixture of distereomers in good yields, even in the presence of other functionalities.

Finally, in order to demonstrate the importance of the presence of the nitro group we report, as representative example, the conversion of the structure **3ka** into the γ-lactame **4** (58% overall yield, Scheme 2) via $HCOONH_4$–Pd/C reduction,[8] by means of both the nitro and the C,C double bond were reduced. Although three stereogenic centers are present, only two diastereomers of the compound **4** were isolated (1:1).



**3ka** **4**

**Scheme 2.** Synthesis of γ-lactame **4** from **3ka**.

Thus, our method represents a new, chemoselective way for the $S_N2'$ reaction of nitroalkanes to dialkyl 2-(bromomethyl)fumarates in which the nitro group can be completely preserved, allowing the formation of a variety of polyfunctionalized adducts. Moreover, we have demonstrated that our procedure can be conveniently applied to the synthesis of an important class of compounds such as γ-lactames.[9]

## Acknowledgments

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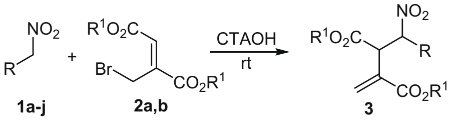
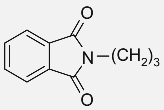
## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.122.

**Table 2**
Adducts **3** prepared



**1a-j** **2a,b** **3**

| R | | $R^1$ | | Reaction time (h) | | Yield[a] (%) of **3**[b] (dr) |
|---|---|---|---|---|---|---|
| Me | **1a** | Me | **2a** | 5 | **3aa** | 75 (67:33) |
| *n*-Bu | **1b** | Me | **2a** | 7 | **3ba** | 70 (68:32) |
|  | **1c** | Me | **2a** | 12 | **3ca** | 68 (61:39) |
| *n*-$C_{11}H_{23}$ | **1d** | Me | **2a** | 7 | **3da** | 65 (84:16) |
| *n*-$C_7H_{15}$ | **1e** | Me | **2a** | 7 | **3ea** | 70 (54:46) |
| $CH_2{=}CH(CH_2)_8$ | **1f** | Me | **2a** | 7 | **3fa** | 64 (63:37) |
| $Me_2(CH_2)_2$ | **1g** | Me | **2a** | 7 | **3ga** | 70 (53:47) |
| $AcO(CH_2)_5$ | **1h** | Me | **2a** | 6 | **3ha** | 60 (51:49) |
| Ph | **1j** | Me | **2a** | 7 | **3ja** | 71 (71:29) |
| $Ph(CH_2)_2$ | **1k** | Me | **2a** | 6 | **3ka** | 66 (60:40) |
| $MeOCO(CH_2)_4$ | **1l** | Et | **2b** | 12 | **3lb** | 67 (72:28) |
| $CH_2{=}CH(CH_2)_8$ | **1f** | Et | **2b** | 12 | **3fb** | 61 (60:40) |
| Ph | **1j** | Et | **2b** | 7 | **3jb** | 70 (53:47) |
| $-(CH_2)_5-$ | **1m** | Me | **2a** | 24 | **3ma** | 44 |

[a] Yield of pure, isolated product.
[b] The diastereomeric ratio was defined by $^1H$ NMR studies.

## References and notes

1. Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971.
2. (a) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833–847; Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1992; pp 321–340; Ono, N. *The Nitro Group in Organic Synthesis*; Wiley VCH: New York, 2001; (d) Ballini, R.; Palmieri, A. *Curr. Org. Chem.* **2006**, *10*, 2145–2169.
3. (a) Seebach, D.; Henning, R.; Lehr, F.; Widdowson, D. A. *Tetrahedron Lett.* **1977**, *18*, 1161–1164; (b) Seebach, D.; Lehr, F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 505–506; (c) Henning, R.; Lehr, F.; Seebach, D. *Helv. Chim. Acta* **1976**, *59*, 2213–2217; (d) Williams, T. M.; Mosher, H. S. *Tetrahedron Lett.* **1985**, *26*, 6269–6272;

(e) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705–1720.

4. Béji, F.; Lebreton, J.; Villiéras, J.; Amri, H. *Tetrahedron* **2001**, *57*, 9959–9962.
5. (a) Gogoi, S.; Argade, N. P. *Tetrahedron* **2004**, *60*, 9093–9097; (b) Kar, A.; Argade, N. P. *Tetrahedron* **2003**, *59*, 2991–2998.
6. Ballini, R.; Fiorini, D.; Gil, M. V.; Palmieri, A. *Tetrahedron* **2004**, *60*, 2799–2804.
7. Ballini, R.; Palmieri, A. *Adv. Synth. Catal.* **2006**, *348*, 1154–1156.
8. Lucet, D.; Sabelle, S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583–2591.
9. See for examples: (a) Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1436–1437; (b) Horni, A.; Hubáček, I.; Hesse, M. *Helv. Chem. Acta* **1994**, *77*, 579–585; (c) Shorvon, S. *Lancet* **2001**, *358*, 1885–1892.