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The Michael Reaction of Nitroalkanes with Conjugated Enones in Aqueous Media

Roberto Ballini,* and Giovanna Bosica

Dipartimento di Scienze Chimiche dell'Università, Via S. Agostino 1, 62032 Camerino, Italy

Abstract: The Michael reaction of various nitroalkanes with conjugated enones can be performed in NaOH 0.025 M and in the presence of cetyltrimethylammonium chloride (CTACl) as cationic surfactant, without any organic solvent. Good yields of the products are obtained even with hindered starting materials. Copyright © 1996 Elsevier Science Ltd

The Michael addition of nitroalkanes to electron-deficient alkenes is a powerful synthetic tool[1] perceiving that the nitro group can be transformed into various functionalities.[2]

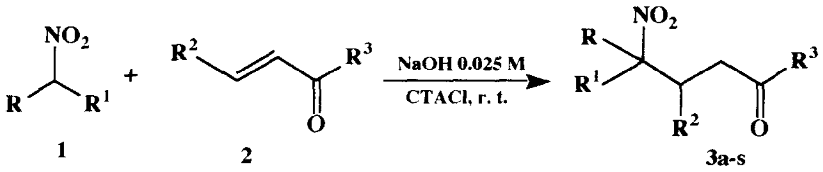
As routine procedure this reaction is performed in the presence of a base. Different organic bases have been used in homogeneous solutions,[3] or, alternatively, some heterogeneous catalysts have been proposed.[4]

The need to reduce the amount toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.[5]

In the recent years there has been increasing recognition that water is an attractive medium for many organic reactions.[6] The aqueous medium with respect to organic solvents is less expensive, less dangerous and environment-friendly, while it allows a right control of the pH. In addition, the low solubility of most reagents in water is not an obstacle to the reactivity which, on the contrary, is often improved.[7]

Recently, Lubineau and Augé[8] published the first example of the Michael addition of nitroalkanes in water with the help of sugars. However, this method seems to be effective only when nitromethane or nitroethane are used as nucleophiles and methylvinylketone (MVK) as the alkene acceptor. Moreover, long reaction times are required, expecially when nitroethane is employed.

With the aim to avoid these limitations we explored several conditions and now we found that this reaction can be dramatically improved in aqueous media using a solution of sodium hydroxide 0.025 M in the presence of catalytic amount of cetyltrimethylammonium chloride (CTACl) as cationic surfactant (Scheme 1). Under these conditions both primary and secondary nitroalkanes easily react with a variety of conjugated enones, even those substituted in the β-position (entry **3o,q-s**, Table 1), and very short reaction times are demanded.



Scheme 1

Table1.

Entry	R	R^1	R^2	R^3	Yield (%)	Reaction time (h)
3a	Me	H	H	Me	85	1
3b	Et	H	H	Me	78	1
3c	*n*-Bu	H	H	Me	83	1
3d	Me	Me	H	Me	75	1
3e	Me	H	H	Et	76	2
3f	Et	H	H	Et	64	1
3g	*n*-Bu	H	H	Et	70	1
3h	Me	Me	H	Et	71	1
3i	Me	H	H	*n*-Pr	68	1
3j	Et	H	H	*n*-Pr	82	1
3k	*n*-Bu	H	H	*n*-Pr	68	2
3l	Me	Me	H	*n*-Pr	77	2
3m	$CH_3(CH_2)_9$	H	H	Me	74	2
3n	$CH_3(CH_2)_9$	H	H	Et	70	2
3o	Me	H	Me	Et	60	15
3p	$-(CH_2)_5-$		H	Me	72	1
3q	*n*-Bu	H	$-(CH_2)_3-$		79	2
3r	Me	H	$-(CH_2)_2$		72	2
3s	*n*-Bu	H	$-(CH_2)_2-$		93	1

Thus, our procedure allows one to perform this important reaction efficiently in an inexpensive and ecological medium; an organic solvent (diethylether) is needed only during the work up, with evident economical and environmental advantages, expecially for widespread industrial use.

We believe that this procedure is an attractive option to the conventional method,[1-4] and could be of high interest for several chemists using this kind of reaction, particularly in the synthesis of important natural products.[9] The potential of this method is now under investigation in our laboratory.

A typical experimental procedure follows: To a mixture of nitroalkane **1** (45 mmol) and the enone **2** (30 mmol), in NaOH 0.025 M (70 ml), was added, at room temperature, cetyltrimethylammonium chloride (CTACl, 3 mmol). The mixture was stirred at room temperature for the appropriate time (TLC, GC, see Table 1), then saturated with NaCl and extracted with Et_2O (4 x 20 ml). The organic phase was dried (Na_2SO_4), concentrated, and the crude product was purified by flash chromatography (EtOAc/cyclohexane, 2:8) or by distillation giving the pure γ-nitro ketone **3**.[10]

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10. All compounds were characterized by spectroscopic methods: **3a**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 1.55 (3H, d, J = 6.5Hz), 2.05-2.17 (2H, m), 2.18 (3H, s), 2.5-2.56 (2H, m), 4.56-4.63 (1H, m). Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.65; H, 7.63; N, 9.65. Found: C, 49.88; H, 7.77; N, 9.58. **3b**:

ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.96 (3H, t, *J* = 7.4Hz), 1.68-2.15 (4H, m), 2.16 (3H, s), 2.5 (2H, t, *J* = 7.2Hz), 4.38-4.52 (1H, m). Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 53.02; H,8.39; N, 8.66. **3c**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.84-0.92 (3H, m), 1.23-1.4 (4H, m), 1.68-2.2 (4H, m), 2.15 (3H, s), 2.45-2.53 (2H, m), 4.43-4.52 (1H, m). Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.64; H, 9.32; N, 7.67. **3d**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 1.58 (6H, s), 2.17 (3H, s), 2.18-2.24 (2H, m), 2.4-2.5 (2H, m). Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 53.07; H, 8.09; N, 8.88. **3e**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 1.05 (3H, t, *J* = 7.3Hz), 1.54 (3H, d, *J* = 6.7Hz), 2.05-2.17 (2H, m), 2.37-2.53 (4H, m), 4.5-4.7 (1H, m). Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.69; H, 8.38; N, 8.94. **3f**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.95 (3H, t, *J* = 7.4Hz). 1.05 (3H, t, *J* = 7.3Hz), 1.7-2.2 (4H, m), 2.36-2.5 (4H, m), 4.32-4.5 (1H, m). Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.70; H, 8.56; N, 7.96. **3g**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.8-0.9 (3H, m), 1.05 (3H, t, *J* = 7.5Hz), 1.23-1.4 (4H, m), 1.92-2.2 (4H, m), 2.38-2.5 (4H, m), 4.45-4.55 (1H, m). Anal. Calcd. for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.39; H, 9.71; N, 7.09. **3h**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 1.03 (3H, t, *J* = 7.3Hz), 1.55 (6H, m), 2.1-2.2 (2H, m), 2.3-2.48 (4H, m). Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.66; H, 8.90; N, 8.00. **3i**: ν_{max} neat/cm^{-1} 1700 and 1540; δ_H ($CDCl_3$) 0.9 (3H, t, *J* = 7.5Hz), 1.53 (3H, d, *J* = 6.7Hz), 1.55-1.65 (2H, m), 2.05-2.16 (2H, m), 2.37 (2H, t, *J* = 7.3Hz), 2.48 (2H, t, *J* =7Hz), 4.54-4.67 (1H, m). Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.29; H, 8.90; N, 7.87. **3j**: ν_{max} neat/cm^{-1} 1700 and 1540; δ_H ($CDCl_3$) 0.85-1.0 (6H, m), 1.5-1.65 (2H, m), 1.9-2.2 (4H, m), 2.3-2.5 (4H, m), 4.35-4.43 (1H, m). Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.91; H, 8.98; N, 7.66. **3k**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.85-0.95 (6H, m), 1.25-1.4 (4H, m), 1.58-1.64 (2H, m), 1.9-2.15 (4H, m), 2.35-2.5 (4H, m), 4.4-4.53 (1H, m). Anal. Calcd. for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.51; H, 10.02; N, 6.33. **3l**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.92 (3H, t, *J* = 7.5Hz), 1.57 (6H, s), 1.55-1.63 (2H, m), 2.15-2.21 (2H, m), 2.34-2.44 (4H, m). Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.87; H, 8.97; N, 7.63. **3m**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.82-0.96 (3H, m), 1.2-1.4 (16H, m), 1.84-2.15 (4H, m), 2.14 (3H, s), 2.43-2.54 (2H, m), 4.4-4.56 (1H, m). Anal. Calcd. for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found: C, 66.54; H, 10.93; N, 5.00. **3n**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.82-0.9 (3H, m), 1.08 (3H, t, *J* = 7.3Hz), 1.15-1.38 (16H, m), 1.88-2.18 (4H, m), 2.34-2.5 (4H, m), 4.4-4.57 (1H, m). Anal. Calcd. for $C_{16}H_{31}NO_3$: C, 67.33; H, 10.95; N, 4.91. Found: C, 67.54; H, 11.12; N, 4.79. **3o**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.92-1.1 (6H, m), 1.48 (1.4 H, d, *J* = 3.0Hz), 1.5 (1.6H, d, *J* = 3.0Hz), 2.3-2.7 (5H, m), 4.5-4.7 (1H, m). Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.68; H, 8.54; N, 7.97. **3p**: ν_{max} neat/cm^{-1} 1700 and 1520; δ_H ($CDCl_3$) 1.2-1.7 (10H, m), 2.05-2.15 (5H, m + s), 2.3-2.45 (2H, m). Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.06; H, 8.78; N, 6.91. **3q**: ν_{max} neat/cm^{-1} 1700 and 1535; δ_H ($CDCl_3$) 0.9 (3H, t, *J* = 6.8Hz), 1.2-2.5 (15H, m), 4.3-4.5 (1H, m). Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.13; H, 9.13; N, 6.43. **3r**: ν_{max} neat/cm^{-1} 1730 and 1540; δ_H ($CDCl_3$) 1.58 (1.5H, d, *J* = 6.6 Hz), 1.61 (1.5H, d, *J* = 6.7Hz), 1.85-2.5 (6H, m), 2.65-2.8 (1H, m), 4.43-4.5 (1H, m). Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.92. Found: C, 53.68; H, 6.88; N, 9.08. **3s**: ν_{max} neat/cm^{-1} 1735 and 1540; δ_H ($CDCl_3$) 0.85-1.0 (3H, m), 1.2-1.45 (6H, m), 1.5-2.5 (6H, m), 2.6-2.84 (1H, m), 4.34-4.47 (1H, m). Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.09; H, 8.77; N, 6.90.

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