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Nitroaldol (Henry) Reaction Catalyzed by Amberlyst A-21 as a Far Superior Heterogeneous Catalyst.

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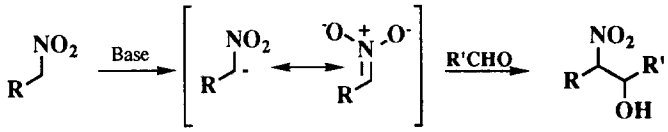
Abstract: β-Nitroalcohols can be efficiently obtained with the help of Amberlyst A-21, as heterogeneous basic catalyst, with or without solvent. This method is far superior to the heterogeneous catalysts previously reported for the nitroaldol (Henry) reaction, in fact it gives higher yields with primary and secondary nitroalkanes, the formation of by-products such as nitroalkenes is avoited even if aromatic aldehydes are used, and it is indipendent from the ratio catalyst/starting materials. Moreover its mildness is demonstrated by the no-epoxidation of bromhydrins.

Nitroalkanes have proved to be useful in complex organic syntheses because of the many possible transformations of the nitro functionality and perhaps, more importantly, because of the variety of carbon-carbon bond forming reactions that proceed under very mild conditions

The nitroaldol (Henry) reaction (Scheme 1) and its variants have been used extensively in carbon-carbon bond formation.[1-9]



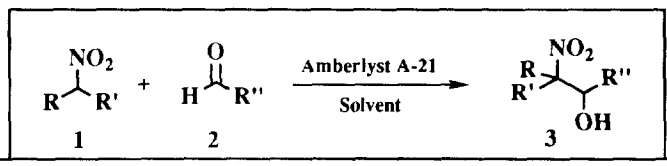
Scheme 1

The classical nitroaldol reaction is routinely performed under basic conditions such as alkali metal hydroxides, carbonates, bicarbonates, alkoxides, calcium and barium hydroxides and magnesium and aluminium ethoxides. Rhodium complex and, among organic bases, primary and tertiary amines and ammonium acetate and fluoride have proved to be useful.[1]

Heterogeneous catalyst has showed to be crucial to chemical technology, and innumerable chemical reactions are facilitates by this catalyst.[10]

Two heterogeneous phase methods have been devised for the Henry reaction, firstly by using commercial chromatographic basic alumina in the absence of a solvent,[11] then with alumina-supported potassium fluoride without solvent.[12] However, the first method,[11] although furnishes good results, requires long reaction time and the presence of nitroalkene, as an elimination by-product, is often observed,[13,14] while the use of alumina/KF requires the preparation of the catalyst, the need (in some cases) of inert atmosphere, and the catalyst/substrate ratio have a marked influence on the yield of β-nitroalkanol, moreover this method has been reported to be efficient only with primary nitroalkanes.

During the synthesis of some natural products, *via* the Henry reaction, we observed[15,16] that the use of Amberlyst A-21 was more effective than alumina and alumina-KF as heterogeneous catalyst, consequently we decided to investigate the potential of this catalyst.



1 2 3

Table II

Entry	Solvent [Yield (%) / Reaction time (h)]			
	CH_2Cl_2	Et_2O	THF	Solvent-free
3e	70/10	82/10	76/9	84/10
3l	82/6	78/3	83/4	85/3
3n	77/6	75/8	80/7	80/7

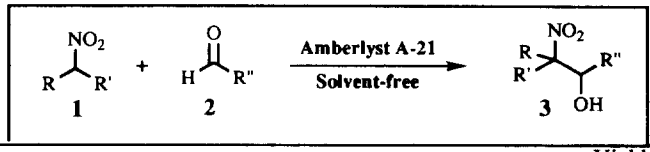
We found that Amberlyst A-21 is far superior as general catalyst for the nitroaldol reaction, in fact it is possible to obtain β-nitroalkanol in high yields (70-95%), by limited reaction times, and from a wide variety of starting materials. The Amberlyst A-21 avoids the dehydration of the 2-nitroalcohols into nitroalkenes even if aromatic aldehydes are used (Entry **3r-v**).

The reaction has been performed by adding 8-10 g of Amberlyst A-21 to 0.05 mole of aldehyde and 0.05 mole of nitroalkane, however, unlike to other methods,[12] the yields are substantially independent from the ratio catalyst/starting materials. It is important to point out that, after recycling, the catalyst can be reused without a considerable loss of the efficiency.

The results reported in Table I refer to the solvent-free reaction, however, as summarized in the Table II, different solvents (Et_2O, CH_2Cl_2, THF) can be used without a substantial change of the yield.

It is important to point out that, by our method, both primary and secondary nitroalkanes give good

Table I



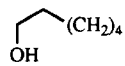
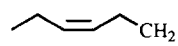
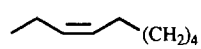
Entry	R	R'	R"	Yield (%)	Reaction time (h)
3a		H	CH_3	70	16
3b		H	CH_3	70	20
3c	CH_3	H		80	18
3d	H	H	$CH_3(CH_2)_5$	80	6
3e	CH_3CH_2	H	$CH_3(CH_2)_5$	84	10
3f	$CH_3(CH_2)_2$	H	$CH_3(CH_2)_5$	83	6
3g	CH_3	CH_3	$CH_3(CH_2)_5$	80	7
3h	CH_3	H		87	6
3i	CH_3	CH_3		80	15
3j	CH_3CH_2	H	$c\text{-}C_6H_{11}$	85	12
3k	H	H	$Ph(CH_2)_2$	85	3

Table I (Contd...)

Entry	R	R'	R''	Yield (%)	Reaction time (h)
3l	CH_3	H	$Ph(CH_2)_2$	85	3
3m	$CH_3(CH_2)_3$	H	$Ph(CH_2)_2$	90	3
3n	CH_3	CH_3	$Ph(CH_2)_2$	83	7
3o	$-(CH_2)_5-$		$Ph(CH_2)_2$	95	9
3p	$CH_3CO(CH_2)_2$	H	$Ph(CH_2)_2$	95	5
3q	Br	H	$Ph(CH_2)_2$	79	6
3r	CH_3	H	2-Furanyl	85	18
3s	CH_3	CH_3	2-Furanyl	77	18
3t	$CH_3CO_2(CH_2)_2$	H	2-Furanyl	76	18
3u	CH_3CH_2	H	Ph	70	18
3v	$CH_3(CH_2)_3$	H	Ph	81	18

results. Compared with other processes our procedure gives, generally, better yields. Moreover, this catalyst does not affect labile functional groups and its mildness is demonstrated by the stability of the bromohydrin **3q** to epoxide formation, under these basic conditions.

We consider that Amberlyst A-21 is one of the most convenient catalyst for the Henry reaction, on the basis of its simplicity, cheapness, and the high yields obtained with a large variety of derivatives, under mild conditions.

Experimental

General. All ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz on a Varian VXR 300; *J* values are given in Hz. IR spectra were recorded with a Perkin Elmer 257 spectrophotometer. The reactions were monitored by TLC. The aldehydes **2**, if necessary, were distilled before the use. Amberlyst A-21 was purchased from Aldrich Co.

General Procedure for the Synthesis of Nitro Alcohol (3), Without Solvent. A 100 ml two-necked flask equipped with a mechanical stirrer was charged with nitro compound **1** (30 mmol) and cooled with an ice-water bath. Aldehyde **2** (30 mmol) was added, and the mixture was stirred for 15 min. Amberlyst A-21 was added (5-7 g), and stirring was continued for the right time (TLC, see Table I). The Amberlyst was washed with CH_2Cl_2 (4 x 25 ml). The filtered extract was evaporated and the crude nitro alcohol **3** was purified by chromatography or used as it is.

General Procedure for the Synthesis of Nitro Alcohol (3e,l,n) with Solvent. The nitro compound **1** (30 mmol) and the aldehyde **2** (30 mmol) were added to the solvent (Table II, 30 ml), then Amberlyst A-21 (5-7 g) was added and the mixture was magnetically stirred for the right time (Table II). After filtration the Amberlyst was washed with the solvent used and the extracts were evaporated. The crude nitroalcohol **3** was purified as above.

3a: IR (film): ν = 3430 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.05-1.4 (6H, m), 1.7-2.48 (4H, m), 3.7-3.9 (1H, m), 4.5-4.8 (1H, m).

3b: IR (film): ν = 3420 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.23-1.45 (10H, m), 1.45-2.00 (5H, m), 3.6-3.7 (2H, t, *J* = 6.2Hz), 4.05-4.25 (1H, m), 4.35-4.48 (1H, m).

3c: IR (film): ν = 3460 and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.88-1.04 (6H, m), 1.2-1.6 (7H, m), 3.88-4.02 (1H, m), 4.55-4.8 (1H, m).

3d: IR (film): ν = 3420 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.88 (3H, t, *J* = 7.2Hz), 1.1-1.7 (10H, m), 4.15-4.45 (1H, m), 4.38 (2H, d, *J* = 6.8Hz).

3e: IR (film): ν = 3400 and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.85 (3H, t, *J* = 7.2Hz), 1.05-1.6 (8H, m), 1.7-2.2 (4H, m), 3.8-4.05 (1H, m), 4.3-4.42 (1H, m).

3f: IR (film): ν = 3400 and 1545 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.85 (6H, m), 1.2-1.4 (9H, m), 1.4-1.6 (2H, m), 1.64-1.85 (2H, m), 1.95-2.2 (2H, m), 3.8-4.05 (1H, m), 4.4-4.55 (1H, m).

3g: IR (film): ν = 3440 and 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.89 (3H, d, *J* =7.2Hz), 1.2-1.75 (10H, m), 4.0 (1H, d, *J* = 9.9Hz).

3h: IR (film): ν = 3440 and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.89-1.02 (3H, t, *J* = 7.2Hz), 1.5-1.6 (3H, d, *J* = 7.2Hz), 2.0-2.3 (6H, m), 4.1 (1H, m), 4.45-4.6 (1H, m), 5.25-5.55 (2H, m).

3i: IR (film): ν = 3420 and 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.9-1.0 (3H, t, *J* = 7.5Hz), 1.2-1.5 (10, m), 1.52-1.55 (6H, d, *J* = 2.5Hz), 1.92-2.09 (2H, m), 3.9-4.05 (m, 1H) 5.2-5.45 (2H, m).

3j: IR (film): ν = 3435 and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.95 (3H, t, *J* = 7.3Hz), 1.0-2.3 (m, 13H), 3.55-3.8 (1H, m), 4.5-4.65 (1H, m).

3k: IR (film): ν = 3340 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.7-1.95 (2H, m), 2.65-2.95 (2H, m), 4.22-4.4 (1H, m), 4.4 (2H, d, *J* = 5.6Hz), 7.12-7.38 (5H, m).

3l: IR (film): ν = 3400 and 1520 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.85 (3H, t, *J* =7.2Hz), 1.05-1.6 (8H, m), 1.7-2.2 (4H, m), 3.8-4.05 (1H, m), 4.3-4.42 (1H, m).

3m: IR (film): ν = 3400 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.9 (3H, *J* = 7.1Hz), 1.2-1.48 (4H, m), 1.65-2.35 (4H, m), 2.62-3.0 (2H, m), 3.8-4.1 (1H, m), 4.35-4.52 (1H, m), 7.15-7.38 (5H, m).

3n: IR (film): ν = 3450 and 1550 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.62 (3H, s), 1.6-1.85 (5H, m + s), 2.6 (1H, m), 2.65-3.05 (2H, m), 4.02 (1H, dd, *J* = 1.9 and 10.2Hz), 7.15-7.4 (5H, m).

3o: IR (film): ν = 3460 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.12-2.18 (10H, m), 2.38-3.0 (4H, m), 3.55-3.7 (1H, m), 7.05-7.35 (5H, m).

3p: IR (film): ν = 3420 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.45-2.35 (4H, m), 2.13 (3H, s), 2.52 (2H, t, *J* = 7Hz), 2.55-3.0 (3H, m), 3.8-4.1 (1H, m), 4.3-4.6 (1H, m), 7.1-7.4 (5H, m).

3q: IR (film): ν = 3400 and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.8-3.0 (5H, m), 4.1-4.3 (1H, m), 5.78 (0.7H, d, *J* = 7.9Hz), 5.96 (0.3, d, *J* = 0.3Hz).

3r: IR (film): ν = 3420 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.4 (2H, d, *J* = 6.6Hz), 1.6 (1H, d, *J* =6.9), 4.8-5.1 (2H, m), 6.35-6.42 (2H, m), 7.4-7.45 (1H, m).

3s: IR (film): ν = 3500 and 1560 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.5 (3H, s), 1.68 (3H, s), 5.28 (1H, s), 6.38-6.4 (2H, m), 7.4-7.42 (1H, m).

3t: IR (film): ν = 3410, 1700 and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.8-2.5 (2H, m), 3.68 (3H, s), 4.9-5.1

(2H, m), 6.35-6.5 (2H, m), 7.4-7.45 (1H, m).

3u: IR (film): ν = 3400 and 1520 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.87 (2.4H, t, *J* = 7.4Hz), 0.94 (0.6, t, *J* = 7.4Hz), 1.3-2.0 (2H, m), 4.5-4.7 (1H, m), 5.03 (0.8H, d, *J* = 9.2Hz), 5.2 (0.2H, d, *J* = 4.8Hz), 7.25-7.45 (5H, m).

3v: IR (film): ν = 3450 and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.7-0.9 (3H, m), 1.0-1.4 (4H, m), 1.75-1.95 (2H, m), 4.55-4.75 (1H, m), 5.02 (0.8H, d, *J* = 4.9Hz), 5.17 (0.2, d, *J* = 4.9Hz), 7.25-7.65 (5H, m).

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