Fast Nitroaldol Reaction Using Powdered KOH in Dry Media

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(Received June 28, 1999; CL-990571)

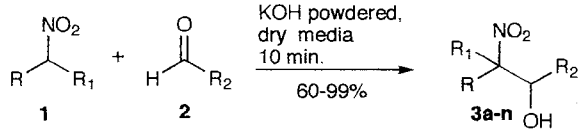
β-Nitroalkanols are easily obtained within a few minutes, through the nitroaldol (Henry) reaction, catalyzed by a stoichiometric amount of powdered potassium hydroxide, in dry media. Satisfactory to excellent yields are obtained both with primary and secondary nitrocompounds, either with aromatic or aliphatic aldehydes.

The nitroaldol (Henry) reaction has became a classical method for the chemical synthesis of carbon-carbon bonds,[1] and has been used in the preparation of diverse natural products.[2] In addition, the versatility of the nitro group provides a facile entry to a wide range of other functionalities.[3]

The classical methods of preparation of 2-nitroalkanols are performed in the presence of a base in an organic solution.[1] Improved procedures have been recently introduced by the use of trialkylsilyl chloride,[4] rhodium complex,[5] and tetramethylguanidine (TMG).[6] However, these methods, although efficient, are laborious,[4] or need a large excess of nitroalkane.[5,6] The latter is a serious drawback, especially when valuable nitro derivatives are employed.

The need to reduce the amount of toxic waste requires increasing emphasis on the use of new synthetic methods.[7] In this context, in recent years there has been a great interest in the nitroaldol reaction mediated by heterogeneous catalyst, using solvent-free conditions. Thus, basic alumina,[8] alumina-supported potassium fluoride,[9] layered zirconium phosphate,[10] Amberlyst A-21,[11] and SiO_2[12] have been proposed for this purpose. Nevertheless, these heterogeneous procedures, even furnish good results, demand long reaction times,[8,10,11] the help of microwave,[12] the tedious preparation of the catalyst,[10] the dependence of the yield from the catalyst/substrate ratio,[9] and/or are not of general applicability since some of these are limited to aliphatic aldehydes,[8] or primary nitroalkanes.[9,10,12] Therefore, the development of new methologies for the preparation of 2-nitroalkanols is very attractive owing to their synthetic value.

Recently, we reported[13] that the Henry reaction can be efficiently performed, in moderate reaction times (2-6 h), in aqueous NaOH 0.025 M, in the presence of cetyltrimethylammonium chloride (CTACl) as cationic surfactant. Based on this previous observation we have now found a new solvent-free condition for a rapid and efficient nitroaldol reaction. In fact, by mixing (with the help of a spatula) the nitroalkane **1**, at 0 °C, to a stoichiometric amount of both aldehyde **2** and powdered KOH the formation of a diastereomeric mixture of the β-nitroalkanols **3** takes place in ten minutes (Scheme 1). The nitroalkanol, which presumably exists as nitronate salt in the reaction mixture, is dissolved in water and then extracted with ether. The reluctance displayed by the bromohydrins **3b,c** towards intramolecular ring closure seems to confirm the presence of a nitronate specie in aqueous solution. The yields, after aqueous work up and flash chromatography purification, are from satisfactory to excellent (60-99%, see Table), and both primary and secondary nitroalkanes give good results either with aromatic and aliphatic aldehydes.



Scheme 1

Table 1. Preparation of β-nitroalkanols

entry	R	R_1	R_2	Yield % of **3**[a]
a	CH_3	CH_3	$CH_3(CH_2)_3$	65
b	Br	H	Ph	99
c	Br	H	Furyl	64
d	$CH_3(CH_2)_2$	H	$CH_3(CH_2)_2$	62
e	CH_3	H	$CH_3(CH_2)_2$	65
f	H	H	$CH_3(CH_2)_3$	70
g	$PhCH_2$	H	$CH_3(CH_2)_2$	60
h	CH_3	H	$CH_3(CH_2)_4$	63
i	H	H	Ph	61
j	Et	H	$CH_3(CH_2)_3$	73
k	CH_3	H	$CH_3(CH_2)_7$	66
l	H	H	$Ph(CH_2)_2$	60
m	CH_3	H	Et	66
n	CH_3	H	Pr	75

[a]Yield of pure, isolated product

The formation of a diastereomeric mixture of **3** seems to be not a problem since the main uses of nitroalkanols are the conversion into α-nitro ketones,[3b] or conjugated nitroalkenes,[14] in which at least one stereogenic center is lost. If a diastereoselective synthesis of nitroalkanols, for specific purposes, is required other procedures are available,[15] however, these methods are highly laborious and/or produce low yields, and are of moderate generality.

Typical procedure: A 100 ml flask was charged with nitro compound **1** (4 mmol) and cooled with an ice-water bath. Powdered KOH (0.22 g, 4 mmol) was added in small portions, by mixing with the help of a spatula for 2 min. Then, aldehyde **2** (4 mmol) was added dropwise. After mixing for 10 min the reaction mixture was cooled by ice bath and then water (10 ml)

and Et_2O (30 ml) were added. After separation of the organic layer the aqueous solution was extracted with Et_2O (2 x 10 ml) and the organic phases were dried ($MgSO_4$) and evaporated to give the crude β-nitroalkanol **3**, which was then purificated by flash chromatography.

This work was supported by the University of Camerino.

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