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Water-promoted organic reactions. Michael Addition of Nitroalkanes to Methylvinylketone under Neutral Conditions

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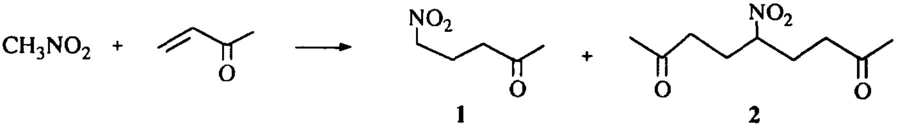
Abstract: Nitromethane and nitroethane when diluted in water, under neutral conditions, react easily , without any catalyst, with Michael acceptors, such as methylvinylketone. The rate of the reaction is enhanced in sugar aqueous solutions.

The Michael reaction is one of the most efficient methods for effecting carbon-carbon formation[1] and has wide applications in organic synthesis[2] and biosynthesis.[3] It is usually carried out with a base as catalyst. But in the presence of strong bases, side-reactions such as secondary condensations, bis-additions, rearrangements and polymerisations are frequently encountered. In recent years various catalysts such as phase-transfer catalysts,[4] transition-metal complexes[5], lanthanides,[6] alumina,[7] lithium iodide,[8] cesium fluoride[9] were proposed to circumvent this problem. All these results strenghthen the idea that the Michael reaction must be carried out with a catalyst to perform nicely, specially when the donor has no basic character. Thus, the addition of nitroalkanes to Michael acceptors, providing a great deal of synthetic intermediates, was abundantly investigated with different catalysts.[10-11]

Independantly, our own research revealed that water as solvent promotes reactions between hydrophobic molecules, for which the volume of activation is negative.[12] According to our postulate, the Michael reaction, which is accelerated under pressure,[13] should be facilitated by water as solvent. Indeed, we discovered that the uncatalyzed Michael reaction of nitromethane and nitroethane with methylvinylketone, considered as impossible[14] since 1916, proceeded nicely, when water, under neutral conditions, was used as solvent, without any catalyst. We have confirmed that the mixture of nitroalkanes and methylvinylketone was unreactive in neat conditions or with usual solvents including dichloromethane, tetrahydrofuran or toluene. In these conditions, a catalyst, such as a base was necessary to achieve the reaction. Moreover, the base-catalyzed Michael reaction of nitromethane with methylvinylketone gave poor yields, unless nitromethane was used in large excess.[15]



1 **2**

Methanol and dimethylsulfoxide, as polar solvents, were investigated as well. The conditions of the reaction are similar to those relative to water as solvent; but, due to the formation of the bis-adduct **2**, the yields in the mono-adduct **1** are low. Thus, whereas the reaction between nitromethane 1 M and methylvinylketone 0.5 M in water went to completion within 32 hours at 40°C, yielding quantitatively a 4/1 mixture of mono and bis-adducts **1** and **2**, as experienced by ^{1}H and ^{13}C NMR spectroscopies; the same reaction carried out in methanol required 5 days at 40°C to afford a 1/1 mixture of **1** and **2**. The selectivity of the water-promoted Michael reaction allows us to propose a useful preparation of 5-nitro-2-pentanone;[16] this selectivity may be regarded as a consequence of the lower water-solubility of **1** compared to nitromethane. As a matter of fact **1** is much more reactive towards methylvinylketone in methanol than in water.

With nitroethane 1M in water, the reaction required 48 hours at 60°C to yield 5-nitro-2-hexanone as the sole product.

Kinetics are under investigation to understand the influence of water. First, it must be pointed out that nitroalkanes are stronger acids in water than in methanol or dimethylsulfoxide,[17] but deprotonation rates (for a given K_{eq}) average approximatively 10^5 faster in dimethylsulfoxide than in water.[19] This could be compensated by a rate-enhancement of the Michael reaction due to the hydrophobic effect. This view is supported by the fact that glucose or saccharose, known to increase the hydrophobic effect,[20] accelerate even more the reaction (see tables 1 and 2). The same accelerating effect of sugar aqueous solutions was observed in many other reactions.[21]

Table 1. Advancement of the Reaction between CH_3NO_2 (1M) and MVK (0,5M) in Water[a] at 40°C

Additive	3 h	6 h	9 h	21 h	32 h
-	-	0.18	0.32	0.61	1
Glucose 4 m	0.26	0.69	1		
Saccharose 2 m	0.28	0.68	1		

Table 2. Advancement of the Reaction between $CH_3CH_2NO_2$ (1M) and MVK (0.5M) in Water[a] at 60°C

Additive	5 h	12 h	18 h	30 h	48 h
-	-	0.16	0.21	0.62	1
Glucose 4 m	0.24	0.38	1		
Saccharose 2.2 m	0.16	0.35	1		

[a] The advancement of the reactions was determined by ^{13}C NMR in a mixture H_2O/D_2O = 90/10.

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