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Uncatalysed intermolecular aza-Michael reactions

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ABSTRACT

The catalyst-free reactions of activated alkenes with primary and secondary amines were investigated leading to various mono- and di-hydroamination products, the latter being rare and original. These reactions were shown to depend first on the strength of the nucleophile. Temperature and steric hindrance of the reagents were the other key factors controlling the selectivity of these aza-Michael reactions. In spite of their poor nucleophilicities, some *N*-heterocyclic amines could react with different activated alkenes affording valuable intermediates. Such results tended to demonstrate the hydrogen-bonding interactions between activated alkenes and poly-nitrogen aromatic cycles may control these concerted or fully conjugate aza-Michael additions.

1. Introduction

Highly selective and atom-economic reactions can be reached using catalysis but challenges remain for some reactions like the synthesis of amines through hydroamination reactions [1]. The aza-Michael reaction involving the reaction of activated alkenes and amines can be considered as a hydroamination reaction. It was largely applied in organic synthesis with the use of various metal or organic catalysts [2]. Surprisingly, the uncatalysed "background" aza-Michael reaction has only been scarcely reported [3,4] and, to the best of our knowledge, no comprehensive study has been carried out so far. Such data could be of interest for highly selective aza-Michael reactions through a rational choice of reagents and experimental conditions. Herein, we would like to report on advantages and limits of uncatalysed aza-Michael reactions. The reactivity scope will be exposed leading to original mono- and di-hydroamination products.

2. Results and discussion

As a start, several weak amine nucleophiles were allowed to react with 10 equivalents of methylvinylketone **1** (Table 1). The use of an excess of alkene to react with an amine is known to increase drastically the conversions; indeed, such a reactivity enhancement was already observed for several catalysed hydroamination reactions of unactivated alkenes [1c,d,g].

In order to check the reactivity issues at a sufficient level of activation, reactions were performed at 100 °C in polar or apolar solvents, respectively tetrachloroethane (TCE) or toluene. Reaction of **1** proceeded with imine **2e** to lead to product **3e** most likely because of higher amine nucleophilicity (entry 5). The use of toluene instead of TCE proved to increase drastically the yield of **3e**, acid traces in TCE decomposing imine **2e**. By comparing reactivity and

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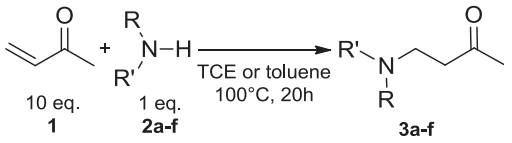
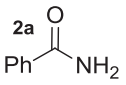
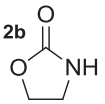
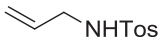
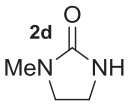
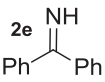
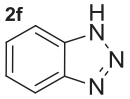
Table 1
Amine reactivity towards methylvinylketone **1**.



Entry	Equivalents of alkene **1**	Amine	Conversion (%)[a]
1	10	**2a** 	0
2	10	**2b** 	0
3	10	**2c** 	0
4	10	**2d** 	0
5	10	**2e** 	77[b]
6	10	**2f** 	100 (79 + 21)[c]
7	2		76 (60 + 16)[c]
8	1		71 (64 + 7)[c]

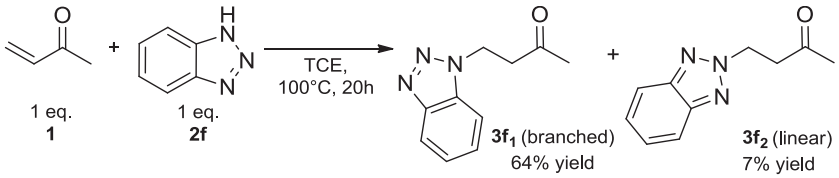
[a] Conversions measured by ^{1}H NMR.
[b] Performed in toluene at 100 °C for 40 h.
[c] Yields of compounds **3f$_1$** (branched) + **3f$_2$** (linear).

pKa values in DMSO of the involved amine reagents, imine **2e** (pKa 31.0) was found to be the strongest nucleophile of that series as compared to benzamide **2a** (pKa 23.3), oxazolidone **2b** (pKa 20.8) or the amines **2c-d,f**. By allowing a 71% yield of products **3f$_1$** and **3f$_2$**, benzotriazole **2f** (pKa 11.9) first appeared to be an exception regarding the poor nucleophilicity of **2f** (Table 1, entry 8 and Scheme 1). It was worth noting the reaction was quantitative as respect to the amine by using 10 equivalents of alkene **1** (entry 6). Moreover, the observed rearrangement of branched product **3f$_1$** into linear product **3f$_2$** was already reported in other syntheses [5].

However, Wang et al. recently described catalyst-free aza-Michael reactions of azoles with β,γ–unsaturated-α-keto esters [3e]. The hydrogen bonding between the carbonyl oxygen of the activated alkene and the NH moiety of the *N*-heterocyclic nucleophile was proposed to form the key reaction intermediate. Then, the fully conjugate nucleophile addition afforded an enol intermediate and later the final addition product after a retro-enolization. Hence, as a general trend, the catalyst-free reactions of amines with activated alkenes appeared to depend on the strength of the nucleophile. Nevertheless, in spite their poor pKas, *N*-heterocyclic amines could react with different activated alkenes affording valuable intermediates. Such results tended to demonstrate the hydrogen-bonding interactions between activated alkenes and such poly-nitrogen aromatic cycles may control these concerted or fully conjugate aza-Michael additions.

Next, we studied the reactivity of acrylate derivatives **4a,b** with primary and secondary amines **2f-s** at 100 °C and 30 °C in toluene. The last was preferred to TCE as far as basic amines proved to be more sensitive to acidic residues of chlorinated solvents (Table 2).

With the exception of amine **2f** which afforded poor yields of compounds **5fa$_1$**, **5fa$_2$** and **5fb$_1$** (entries 1–2), the reactions proceeded quite well for secondary amines **2i-k** at 100 °C affording mono-hydroamination products **5ia**, **5ib**, **5ja** and **5ka** in good yields (entries 3–6). For these last products, yields were quite low at 30 °C except for reaction with *N*-methylbenzylamine **2k** (entry 6). Regarding *N*-methylaniline **2l** and diisopropylamine **2m** (entries 7,8), no conversion was obtained. On the whole, these results confirmed that the less the nitrogen atom was hindered, the more the hydroamination reaction was enabled. The reactivity of primary amines **2n-t** with acrylates **4a,b** was then investigated in detail. At 100 °C, mono-hydroamination **5(n-t)a** and di-hydroamination **6(n-t)a** products were obtained with average to good yields (entries 9–16). It was worth noting methyl crotonate **4b** afforded only mono-hydroamination product **5pb** (entry 12) and aniline **2q** did not react (entry 13). Strikingly, cyclohexylamine **2o**, tertiobutylamine **2s** led selectively to mono-hydroamination products **5oa** and **5sa** (entries 10, 15) whereas butylamine **2r** and methylamine **2t** afforded only di-hydroamination products **6ra** and **6ta** (entries 14, 16). Hence, we could state a sterically bulky primary amine reagent would privilege a mono-hydroamination product whereas a less hindered amine would mainly lead to a di-hydroamination product. However, γ-substituted activated alkenes would offer exclusively mono-hydroamination products. Moreover, lowering the temperature to 30 °C induced the selective formation of mono-hydroamination compounds **5na**, **5oa**, **5pa** and **5ra** but in low yields (entries 9–11, 14). The use of a large excess of alkene **4a** proved to be crucial in order to reach average to good yields of mono-hydroamination product **5pa** and di-hydroamination product **6pa** (entries 11, 17–19). To the best of our knowledge, such results are rare examples of controlled di-hydroamination reactions [6].



Scheme 1.