



Uncatalyzed, green aza-Michael addition of amines to dimethyl maleate



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ARTICLE INFO

Article history:

Received 15 March 2014

Received in revised form 17 June 2014

Accepted 30 June 2014

Available online 4 July 2014

Keywords:

Dimethyl maleate
aza-Michael reaction
Mono-adduct
Solvent-free
Catalyst-free

ABSTRACT

Dimethyl maleate was found to be a very reactive and selective acceptor for the aza-Michael addition in comparison to other commonly used electron-deficient alkenes. It reacts efficiently with a variety of aliphatic amines in complete absence of any catalyst and solvent at room temperature. Under these environmentally-friendly conditions, high yields of selectively mono-adducts were obtained within short reaction times.

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1. Introduction

In recent years significant attention has been given to the development of efficient and operationally simple protocols for carbon–carbon and carbon–heteroatom bonds formation, aimed at the construction of valuable molecules. Elimination of volatile and harmful organic solvents is an important target of green chemistry to prevent solvent wastes, hazards and toxicity and to make syntheses simpler, saving energy.¹ Uncatalyzed reactions can offer a step forward in this direction being interesting ways of carrying on more eco-sustainable synthetic methodologies.² Thus, the development of efficient procedures for useful chemical transformations without any solvent and any catalyst is highly appreciated.

The aza-Michael reaction is considered a very efficient and versatile method of creating new C–N bond³ and one of the shortest routes to β -amino carbonyl derivatives, which have become increasingly important to the natural product and pharmaceutical areas. In fact, it is one of the most widely used reactions in modern organic synthesis of biologically active compounds and being a conjugate addition it benefits from good atom economy.⁴ Moreover aza-Michael addition is of remarkable significance in asymmetric synthesis as documented by the various asymmetric aza-Michael protocols available to perform this reaction in highly

stereoselective manner as well as applied to the total synthesis of natural products.^{4g,5}

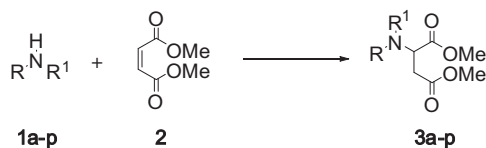
Typical procedures for aza-Michael reactions require strong acid or base catalysts, which are harmful to the environment and produce undesirable by-products.⁶ Much work has been carried out on the aza-Michael addition and a variety of novel catalytic systems and conditions have been reported in the literature, mainly aiming at further improving the green credentials of this reaction class.⁷ Such innovations include, among others, the use of lanthanide derivatives,⁸ silica-supported acids,⁹ resins,¹⁰ clay-supported Lewis acids,¹¹ organic polymers,¹² task-specific ionic liquids,¹³ and reactions in water¹⁴ or solvent-free.¹⁵ Although some improvements, many of the above procedures still require harsh reaction conditions, expensive catalysts, long reaction times, use of hazardous organic solvents and excess amount of Michael acceptors, with poor selectivity, all features, which are not desirable from a green chemistry point of view. Most of the reported methods have focussed on the addition of secondary aliphatic amines or, at times, aromatic amines and the few non-catalytic aza-Michael reactions are restricted to electron-poor acceptors with terminal double bonds or very active double bonds, or else highly nucleophilic aliphatic amines.^{16,3a}

Dimethyl maleate (**2**) is a high versatile Michael acceptor, having two electron withdrawing groups in α - and β -position, which easily allow to access multi-functionalized final adducts.¹⁷ To the best of our knowledge only a very limited number of aza-Michael additions using dimethyl maleate have previously been reported, which, whereas has previously been shown to be suitable acceptor

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for Michael addition with nitro compounds, under different basic catalysts.¹⁸ Among the few examples of aza-Michael additions with dimethyl maleate, and mainly different alkyl fumarates, there are procedures, which require the prior preparation of an ionic liquid catalyst using harsh chemicals and an excess of Michael acceptor,¹⁹ or organic solvents like ethanol at 0 °C and pyridine and triethylamine at 100 °C, to overcome the insolubility in organic solvents of methylamine hydrochloride, used as nucleophile in excess,²⁰ while neat conditions for 24 h at room temperature or for 10 h under refluxing are reported with a few amines only.²¹ Whereas some other procedures refer to regioselective additions to unsymmetrical alkyl fumarates under high temperatures and with long reaction times²² or require an additional inert atmosphere.²³ Overall mostly of these have a finite scope of substrates since their main target is the synthesis of specific compounds like aminoacids, polycarboxylates with surfactant properties and unsaturated polyester resins.^{20,23}

Following our previous studies on solvent-free and uncatalyzed aza-Michael additions,^{24,16c} herein we report a green aza-Michael reaction between dimethyl maleate and different amines (**1a–p**) under neat conditions, without any catalyst and solvent, at room temperature (Scheme 1).



Scheme 1. aza-Michael addition of amines to dimethyl maleate.

2. Results and discussion

A series of screening reactions using 1-pentylamine (**1a**), as the nucleophile, and **2**, as the Michael acceptor, were used in order to determine the most efficient conditions for reaction. All reactions were performed on a 0.01 mol scale of the reagents in stoichiometric ratio. A variety of catalysts were tested with both acetonitrile and THF as solvent. All of the reactions resulted in excellent yield of mono-adduct (**3a**) within a relatively short reaction time (Table 1). It is also of note that the reaction was, in all cases,

Table 1
Model reaction between 1-pentylamine (**1a**) and dimethyl maleate (**2**)

Entry	Catalyst	Solvent	Temp	Time (h)	Yield ^b 3a (%)
1	DBU (1 equiv)	Acetonitrile	rt	5	95
2	DBU (1 equiv)	THF	rt	5	96
3	DBU (0.1 equiv)	Acetonitrile	rt	5	95
4	K ₂ CO ₃ (1 equiv)	Acetonitrile	rt	6	90
5	K ₂ CO ₃ (0.1 equiv)	Acetonitrile	rt	6	88
6	[DBU][Ac] (1 equiv)	/	rt	7	72
7	[DBU][Ac] (0.1 equiv)	/	rt	7	75
8	Al ₂ O ₃ (acidic, 1 equiv)	THF	rt	8	80
9	Al ₂ O ₃ (weakly acidic, 1 equiv)	THF	rt	10	83
10	Amberlyst A-21 (1 equiv)	THF	rt	6	97
11	Amberlyst 15 (1 equiv)	THF	rt	6	96
12	/	/	rt	4	96
13 ^a	/	/	rt	4	95
14	/	/	50 °C	4	97
15	/	THF	rt	6	88
16	/	Acetonitrile	rt	5.5	92

^a Ratio of amine:acceptor was 1.2:1.

^b Yield of pure isolated product.

selective towards the mono-adduct, with no bis-adduct detected under any of the conditions. Much to our surprise, the neat reaction carried out in absence of both catalyst and solvent at room temperature also resulted in an excellent yield of 96%, within 4 h (entry 12, Table 1).

One notable observation was that when the reaction was carried out in absence of solvent and catalyst, the isomeric dimethyl fumarate precipitated out of the reaction after a few minutes. However it was not found to hinder the aza-Michael addition in any way since the reaction between dimethyl fumarate and the amine proceeds efficiently to result in the same mono-adduct.

On recognising that such mild conditions resulted in high yields of solely mono-adduct, we decided to explore whether they would have been suitable for other amines, and a variety of different amines (**1b–p**) were reacted with **2** (Table 2). Other linear aliphatic primary amines gave similar results, with yields ranging from 87% to 97% (entries 1, 3, 10, Table 2), as well as the secondary aliphatic amine tested, dibutylamine (entry 7, Table 2), with 72% yield within 7 h of reaction. The cyclic (entries 9 and 11, Table 2) and branched (entries 2, 4, 5, 6 and 8, Table 2) aliphatic primary amines also resulted in good yields within relatively short reaction times. One anomaly was the low yield obtained using isopropyl amine (entry 2, Table 2)—this was probably due to the volatility of the amine. No reaction was observed with the aromatic amines (entries 13–15, Table 2) used, after 24 h of stirring at room temperature in absence of solvent and catalyst. Although the reaction with aniline (entry 13, Table 2) was warmed to 50 °C for two extra hours and later mixed with 1 equiv of DBU in acetonitrile, none of these conditions elicited any observable reaction.

Table 2
aza-Michael addition of various amines (**1b–p**) to dimethyl maleate (**2**)

Entry	R ¹	R ²	Time (h)	Yield ^b 3 (%)
1	<i>n</i> -C ₃ H ₇ (1b)	H	4	97
2	(CH ₃) ₂ CH (1c)	H	6	52
3	<i>n</i> -C ₄ H ₉ (1d)	H	5	87
4	C ₂ H ₅ CH(CH ₃) (1e)	H	5	85
5	(CH ₃) ₂ CHCH ₂ (1f)	H	6	68
6	(CH ₃) ₃ C (1g)	H	7	65
7	<i>n</i> -C ₄ H ₉ (1h)	<i>n</i> -C ₄ H ₉	7	72
8	(CH ₃) ₂ CHC ₂ H ₄ (1i)	H	4	70
9	<i>c</i> -C ₅ H ₉ (1j)	H	5.5	67
10	<i>n</i> -C ₆ H ₁₃ (1k)	H	4	94
11	cy-C ₆ H ₁₁ (1l)	H	5	78
12	C ₆ H ₅ CH ₂ (1m)	H	6	62
13 ^a	C ₆ H ₅ (1n)	H	24	NR
14	C ₆ H ₅ (1o)	CH ₃	24	NR
15	<i>p</i> -(C ₂ H ₅)C ₆ H ₄ (1p)	H	24	NR

NR='no reaction'.

^a After 24 h, the reaction was heated to 50 °C for 2 h and then 1 equiv of DBU in acetonitrile was added.

^b Yield of pure isolated product.

Under the same neat reaction conditions other typical Michael acceptors (**4**) were then tested with hexylamine (**1k**), to compare the results with those obtained using dimethyl maleate. As can be seen in Table 3, they performed very differently to dimethyl maleate and the results were highly dependent on the structure of the acceptor. Methyl acrylate (**4a**) and acrylonitrile (**4b**) resulted in a high percentage conversion of starting material with a much longer reaction time (20 h). In both cases, the result was a mixture of both mono- (**5**) and bis-adduct (**6**). Other acceptors tested were much less reactive: *trans*-methyl crotonate (**4c**) gave a yield of 60%

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