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Aza-Michael addition of chiral hydrazines to alkylidene malonates

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Abstract—The conjugate spontaneous addition of chiral *N*,*N*-dialkylhydrazines **1** to dimethyl alkylidene/arylidene malonates **2**, **5**–**10** affords the corresponding β-hydrazino esters in moderate-to-good yields and selectivities. D-Mannitol-derived hydrazine **1a** afforded best results, mainly due to the higher stability of the products **3**, **11**–**16**.

1. Introduction

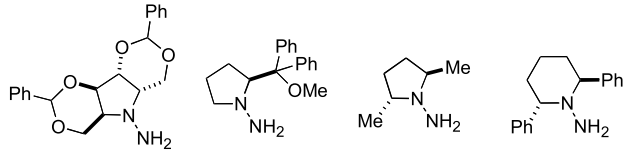
During the last years the interest for β-aminoacids has grown notably due to their presence in a number of natural products and to their application as precursors of other interesting compounds, such as β-lactams.[1] Among the different approaches described for the stereoselective synthesis of β-aminoacids, the aza-Michael addition of ammonia equivalents to α,β-unsaturated carboxylates appears as one of the more attractive methods for its simplicity. Pyrrolidine derived chiral hydrazines have been previously used as neutral nitrogen nucleophiles in the Lewis acid catalyzed 1,4-addition to reactive Michael acceptors as α,β-unsaturated sulfones,[2] and sulfonates.[3] However, the extension of the methodology to α,β-unsaturated esters has not been reported. The use of lithiated *N*-silylhydrazines as ammonia equivalents in their addition to prochiral enoates has been reported instead, but the procedure requires protection and activation of the nucleophile, and strong basic conditions are associated with anionic reagent.[4]

The enhanced electrophilic reactivity provided by the geminal carboxylate functions in alkylidene malonates has been frequently exploited in the conjugate nuclephilic addition of weak nucleophiles under mild conditions.[5] Additionally, these substrates are easily available through Knoevenagel condensation of malonates and carbonyl compounds and due to the presence of identical carboxylate groups, do not require any considerations regarding *E*/*Z* isomerizations.

On the other hand, the precedent of the spontaneous addition of chiral hydrazines to nitroalkenes,[6] which exhibit similar levels of reactivity to that of alkylidene malonates,[7] suggests that the addition of chiral *N*,*N*-dialkylhydrazines to the latter should also be possible under non-catalyzed conditions or at least, under mild conditions compatible with the use of free hydrazines as the nucleophiles. We now wish to present the results collected on the basis of this hypothesis.

2. Results and discussion

Preliminary reactivity experiments were carried out using several chiral hydrazines based in different types of cyclic dialkylamino auxiliaries. These include D-mannitol-derived hydrazine **1a**,[8] (*S*)-1-amino-2-(1-diphenylmethoxymethyl)-pyrrolidine **1b**[9] as a sterically demanding proline derivative, and other C_2-symmetric hydrazines such (*R*,*R*)-1-amino-2,5-dimethylpyrrolidine **1c**[10] and (*S*,*S*)-1-amino-2,5-diphenylpyperidine **1d**[11] (Fig. 1).



1a 1b 1c 1d

Figure 1. Chiral hydrazines **1a**–**d** used in the preliminary screening.

Keywords: Conjugate addition; Hydrazines; Synthetic methods.
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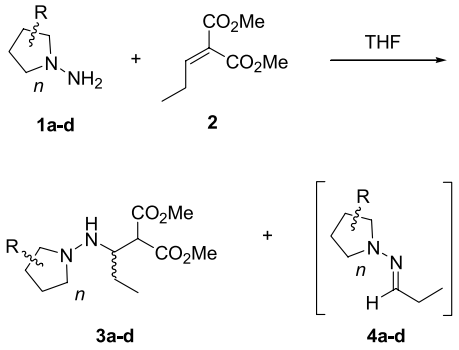
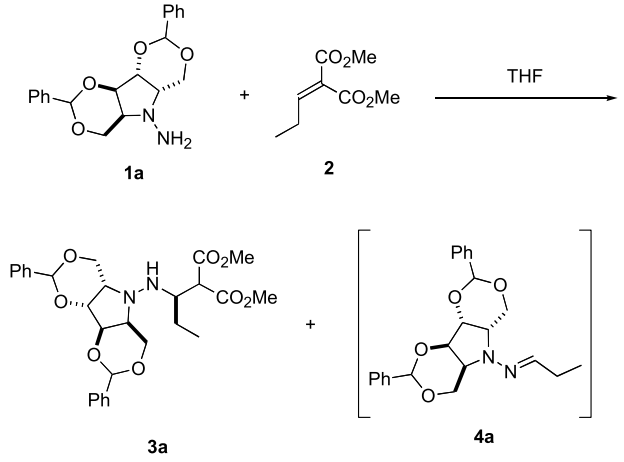
Addition experiments carried out with hydrazines **1a–d** and 2-propylidene malonic acid dimethyl ester **2** confirmed the expected reactivity, as the conjugate addition took place in the absence of promoter or catalyst in all cases. Though the reactivities exhibited by the different hydrazines tested were similar, D-mannitol-derived hydrazine **1a** proved to be the reagent of choice, mainly due to the higher stability of the obtained adduct. On the other hand, adducts obtained from hydrazines **1b–d** showed a higher tendency to suffer a side-reaction to give hydrazones **4b–d**. These by-products, presumably formed by β-elimination of dimethylmalonate, can be viewed as the condensation products of the different hydrazines **1a–d** used with propionaldehyde, formally resulting from a retro-Knoevenagel reaction from **2** (Scheme 1).



Scheme 1. Additions of hydrazines **1a–d** to propylidene dimethylmalonate **2**.

Therefore, a further optimization of the reaction conditions was carried out using hydrazine **1a** and alkylidene malonate **2** as reactants (Scheme 2). The effect of some Lewis acids [MgI_2, $ZnCl_2$, $Zn(TfO)_2$ and $Mg(TfO)_2$], added in catalytic or stoichiometric amounts, was investigated in reactions carried out in THF at room temperature. Though faster additions were observed in all cases, these species also favoured the undesired β-elimination side-reaction, leading to mixtures containing adduct **3a** and hydrazone **4a** in variable amounts. On the basis of these results the effect of different parameters as the solvent and the temperature on the non-catalyzed addition was studied.



Scheme 2.

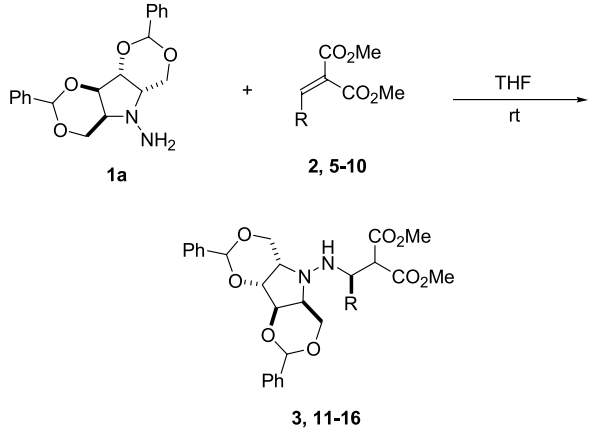
The results collected in Table 1 indicate that THF provides the best result (entry 1), leading to a similar yield (70%) but better diasteroselectivity (d.r.=4:1) than other solvents such as toluene, diethyl ether, methylene chloride or DMF (entries 2–5). Interestingly, the reaction performed in the latter (Table 1, entry 5) resulted in a reversion of the stereoselectivity (d.r. 1:1.8). The undesired β-elimination reaction leading to **4a** was only observed when the reaction was performed in MeOH. Although **3a** was also initially formed in this solvent, this compound was spontaneusly transformed into hydrazone **4a** and dimethyl malonate, observed as the only isolable products after consumption of the starting material.

Table 1. Addition of hydrazine **1a** to dimethyl propylidene malonate **2** in different solvents[a]

Entry	Solvent	Time (h)	Yield of **3a**[b] (%)	d.r.[c]
1	THF	4	70	4:1
2	Toluene	5	68	2:1
3	Et_2O	12	65	2.4:1
4	CH_2Cl_2	4	62	2.5:1
5	DMF	7	68	1:1.8

[a] Reactions performed at room temperature with a 1:1.5 hydrazine:ester ratio.
[b] Overall yield of the product after chromatographic purification.
[c] Determined by ^{13}C NMR analysis of the reaction mixtures.

On the other hand, experiments performed at lower temperatures (0 or −40 °C) resulted in similar yields and selectivities. Therefore, the extension of the procedure to other substrates was carried out at room temperature to get faster reactions. The optimized conditions (THF, room temperature) were applied to the addition of hydrazine **1a** to other aliphatic (**2**, **5**, **6**) and aromatic (**7–10**) alkylidene malonates (Scheme 3). The reactions were carried out using hydrazine **1a** as limiting reagent and 1.1 equiv of alkylidene malonates for the most reactive substrates **2**, **5** and 1.5 equiv in the case of the less reactive **6–10**. Yields



Comp.	**2,3**	**5,11**	**6,12**	**7,13**	**8,14**	**9,15**	**10,16**
R	Et	Me	^{i}Pr	Ph	2-naphthyl	*p*-$C_6H_4NO_2$	4-biphenyl

Scheme 3. Addition of hydrazine **1a** to alkylidene and arylidene malonates **2**, **5–10**.