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# Decarboxylative Amination of SMAHOs by Dialkyl Azodicarboxylates

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The decarboxylative addition of substituted malonic acid half oxyesters (SMAHOs) to dialkyl azodicarboxylates is described. The reaction was promoted by 1,4-diazabicyclo[2.2.2]octane (DABCO) as an organocatalyst in heated toluene. High yields of the coupling products were generally obtained, and the scope of the reaction proved rather important with the potential presence of functionalized side chains at the α-position, affording an original access to α-aminoester derivatives.

## Introduction

Carbon-Nitrogen bond forming reaction has always constituted an important area of research in organic chemistry, due to the ubiquitous presence of nitrogen in most natural or unnatural bioactive compounds.[1–3] In this context, dialkyl azodicarboxylates represent very interesting nitrogen sources, because they are often very affordable and offer the opportunity of designing original synthetic strategies, due to the inherent electrophilicity of the nitrogen atoms they embed.[4] Dialkyl azodicarboxylates are known since a long time[5] and have been used in several C–N bond forming reactions such as their hydroacylation by aldehydes,[6–8] or the C–H amination of heterocyles.[9–10] They also constitute efficient reagents for the α-amination of carbonyl compounds,[11–14] and had thus been used in the enantioselective α-amination of aldehydes using a variety of organocatalysts.[15–18] As a consequence of their smooth reactivity, the use of dialkyl malonates and related compounds in C–N bond forming reactions with dialkyl azodicarboxylates has long constituted a central playground for the organic chemist.[19–21] However, whereas several contributions describe the stereoselective addition of cyclic ketoesters to the N=N bond,[22–32] reactions employing acyclic β-dicarbonyl compounds bearing side chains at the α position are more unusual.[33–35] Therefore, at the beginning of the 2000s, Jørgensen and coworkers described the enantioselective amination of α-substituted β-ketoesters employing a Cu(II) bis-oxazoline complex and furnishing the coupling products in high yields and enantiomeric excesses.[36] A few years later, Bellemin-Laponnaz, Gade and coworkers focused on the effects of oxazoline-derived ligands distortion on copper-catalyzed amination of α-methyl substituted β-keto ester by dibenzyl azodicarboxylate.[37–38] In 2009, Shibasaki and coworkers also described the enantioselective amination of β-amido esters using a lanthanum-based ternary catalyst.[39] A lanthanide / pybox complex was also used by Vallribera and coworkers for the α-amination of acyclic β-ketoesters.[40] Very recently, Guin and coworkers wrote out a very comprehensive study focusing on the enantioselective α-amination of β-dicarbonyl compounds catalyzed by a chiral NHC.[41]

Reactions involving decarboxylative processes are even more rare. An original example of decarboxylative addition of acyclic α-substituted β-dicarbonyl compounds to dialkyl azodicarboxylates was reported by Tan and coworkers in 2011.[42] In this work, a substituted malonic acid half thioester (SMAHT) was added to diethyl azodicarboxylate (DEAD) in the presence of a chiral organocatalyst, furnishing the coupling products in high yields and *ees*. Ma and coworkers also contributed to the field with the organocatalyzed amination of β-keto acids using diisopropyl azodicarboxylate.[43] However, only the use of cyclic compounds was mentioned.

In this context, the decarboxylative amination of substituted malonic acid half oxyesters (SMAHOs) by dialkyl azodicarboxylates, has, to the best of our knowledge, never been described. Such couplings would however represent an alternative route for the straightforward access to unnatural α-amino acids. Therefore, as a part of our ongoing interest on the reactivity and synthetic use of SMAHOs,[44] we describe herein the first example of decarboxylative additions of SMAHOs to dialkyl azodicarboxylates.

## Results and Discussion

The initial optimization sequence was conducted with di-*tert*-butyl azodicarboxylate **1a** and SMAHO **2a** as model reagents. Therefore, **1a** and **2a** were stirred overnight in the presence of a catalyst. Results are presented in Table 1. A first attempt conducted in the presence of a copper catalyst in DMF did not lead to the expected results, a complex mixture of products being obtained after 14 h at 80 °C (Entry 1). We decided to switch to organocatalysis by using a substoichiometric amount

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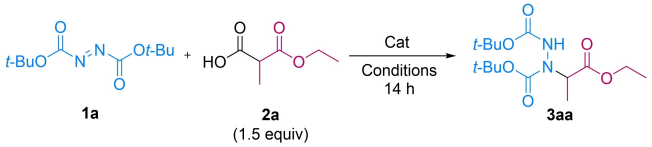
**Table 1.** Optimization of the reaction conditions.[a]

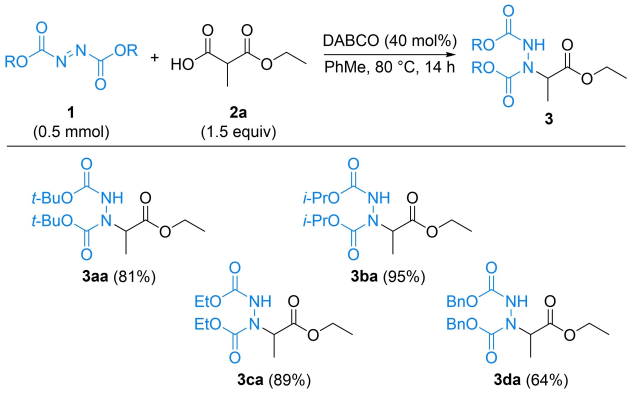



| Entry | Cat (mol%) | Solvent | T (°C) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ (30) | DMF | 80 | –[c] |
| 2 | morpholine (40) | PhMe | 80 | 19 |
| 3 | $NEt_3$ (40) | PhMe | 80 | 21 |
| 4 | quinine (40) | PhMe | 80 | 50 |
| 5 | DBU (40) | PhMe | 80 | 35 |
| **6** | **DABCO (40)** | **PhMe** | **80** | **99 (81)**[d] |
| 7 | DABCO (40) | PhMe | 110 | 82 |
| 8 | DABCO (40) | PhMe | 20 | – |
| 9 | – | PhMe | 80 | – |
| 10 | DABCO (20) | PhMe | 80 | 99 (80)[d] |
| 11 | DABCO (40) | THF | 80 | 60 |
| 12 | DABCO (40) | DMF | 110 | 49 |

[a] Reactions performed with **1 a** (0.5 mmol) and **2 a** (1.5 equiv). [b] GC yield determined using mesitylene as an internal standard. [c] Complex mixture. [d] Isolated yield.

of different amines, which had already provided interesting results in similar reactions involving the decarboxylative addition of SMAHOs to C=N bonds.[45][46] In this case, triethylamine, morpholine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proved able to catalyze the reaction, although in a limited extent (Entries 2–4). A similar limited conversion was noted when using quinine as a catalyst, thus hampering the development of an asymmetric version of the reaction (Entry 5). However, a very significant improvement was observed when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as the amine, a 81% isolated yield being obtained after 14 h at 80 °C (Entry 6). Attempts to increase or decrease the reaction temperature led to deceiving results (Entries 7 and 8), thus confirming that heating at 80 °C was the best compromise. We also verified that the presence of a catalyst was mandatory by performing the reaction in the absence of a base (Entry 9). In this case, no coupling product was observed after heating overnight. Nevertheless, the amount of DABCO could be reduced to 20 mol% with only a limited influence on the isolated yield (Entry 10). Finally, we assessed the possibility of using alternative solvents but either THF (Entry 11) or DMF (Entry 12) gave less efficient couplings.

Under the optimized conditions, reported in entry 6 of Table 1, we first evaluated the azodicarboxylate scope of the reaction using SMAHO **2 a** as the model nucleophile (Scheme 1). These experiments indicated that a range of azodicarboxylates, including diisopropyl azodicarboxylate **1 b**, diethyl azodicarboxylate **1 c** and dibenzyl azodicarboxylate **1 d** were useable in the reaction, furnishing the coupling products in good to excellent yields.




**Scheme 1.** Azodicarboxylate scope of the reaction. Yields of isolated products. Reaction conditions: **1** (0.5 mmol), **2 a** (1.5 equiv), DABCO (40 mol%), PhMe (0.1 M), 80 °C, 14 h.

The influence of the ester part of SMAHOs was then evaluated. In this purpose, the coupling efficiency of SMAHOs bearing different alkyl ester chains was assessed in their reaction with di-isopropyl azodicarboxylate **1 b** (Scheme 2). Therefore, when switching progressively from a methyl- (**3 bb**) to an ethyl- (**3 ba**) and a phenyl ester (**3 bc**), the observed yields decreased concomitantly, indicating that the steric hindrance of the ester plays a significant role on the reactivity. Nevertheless, functional groups such as an allyl (**3 bd**, 72%) or an ester group (**3 be**, 63%) could be introduced at this position, but no reaction occurred with an amide-derived hemimalonate.

The influence of the α-substituent of the starting SMAHO on the reaction fate was next evaluated, also using di-isopropyl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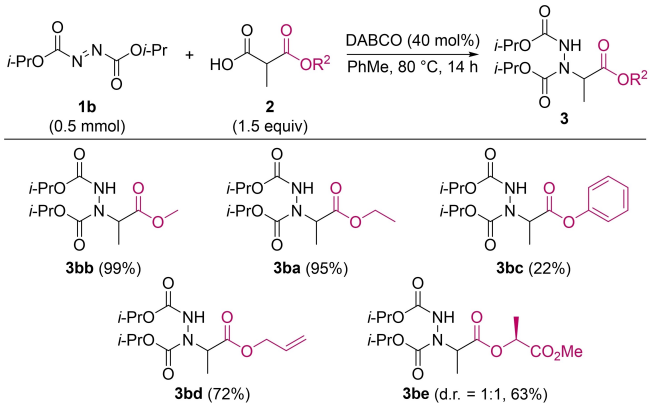
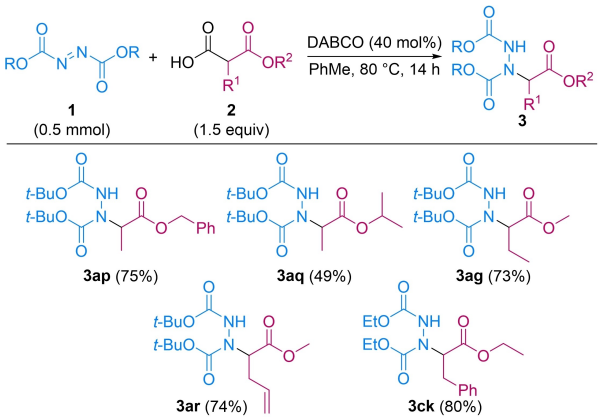
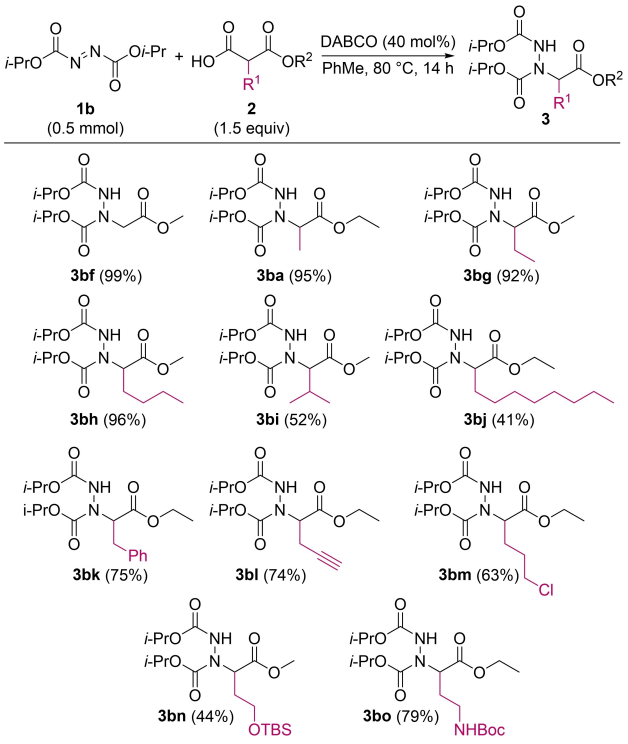



**Scheme 2.** Influence of the ester part of SMAHO on the reaction. Yields of isolated products. Reaction conditions: **1 b** (0.5 mmol), **2** (1.5 equiv), DABCO (40 mol%), PhMe (0.1 M), 80 °C, 14 h.




**Scheme 4.** Miscellaneous experiments. Yields of isolated products. Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv), DABCO (40 mol%), PhMe (0.1 M), 80 °C, 14 h.

azodicarboxylate **1 b** as the electrophilic partner (Scheme 3). These experiments showed a slight steric influence of the α-side chain on the reaction yield, in particular when a very long aliphatic chain is connected to the malonic acid half oxyester. Indeed, high yields were obtained with SMAHOs bearing no (**3 bf**, 99%) or short substituents (Me: **3 ba**, 95%; Et: **3 bg**, 92%; Bu: **3 bh**, 96%), whereas the presence of an *iso*-propyl group (**3 bi**, 52%) or a *n*-octyl chain (**3 bj**, 41%) led to lower yields and no reaction occurred with a phenyl-substituted MAHO. Interestingly, we could notice that functionalized side chains can be used without important loss of efficiency. This is the case of benzyl-substituted MAHO (**3 bk**, 75%) or substituents bearing an alkyne (**3 bl**, 74%), a halogen (**3 bm**, 63%), a protected alcohol (**3 bn**, 44%) or a Boc protected amine (**3 bo**, 79%).




**Scheme 3.** Influence of the α-substituent of SMAHO on the reaction. Yields of isolated products. Reaction conditions: **1 b** (0.5 mmol), **2** (1.5 equiv), DABCO (40 mol%), PhMe (0.1 M), 80 °C, 14 h.

Miscellaneous experiments were also performed with di-*tert*-butyl azodicarboxylate **1 a** and diethyl azodicarboxylate **1 c** (Scheme 4), and confirmed the tendencies discussed above. Therefore, starting from **1 a**, it was shown that SMAHO bearing a benzyl ester (**3 ap**, 75%) as well as those with an ethyl (**3 ag**, 73%) or an allyl (**3 ar**, 74%) substituent on the α position delivered good yields of the coupling products. However, an *iso*-propyl ester led to a decrease of the reaction efficiency (**3 aq**, 49%). The steric influence of the side chain was not so important when starting from **1 c**, and the reaction performed with benzyl SMAHO **2 k** afforded a good 80% yield of the expected product **3 ck**.

## Conclusions

In conclusion, we show that substituted malonic acid half oxyesters (SMAHOs) are relevant nucleophilic partners in the organocatalyzed decarboxylative C–N bond forming reaction by addition to dialkyl azodicarboxylates. The reaction proved general and various reagents could be used with good efficiencies, the only limitation being the presence of very hindered substituents on the SMAHO. These examples illustrate the even growing interest of SMAHOs as nucleophiles in an extended range of more eco-compatible couplings leading to nitrogen containing compounds.

## Supporting Information

The authors have cited additional references within the Supporting Information.[47]



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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** SMAHO · decarboxylation · amination · organocatalysis · aminoacid

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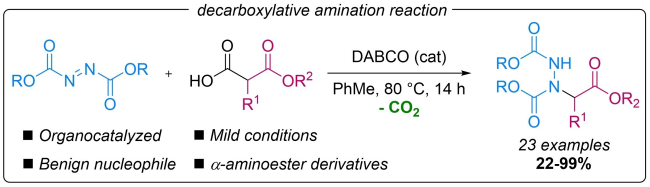


The organocatalyzed decarboxylative addition of substituted malonic acid half oxyesters (SMAHOs) to dialkyl azodicarboxylates led to the formation of α-aminoester derivatives. The reaction can be performed under mild reaction conditions using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst and displayed a rather important scope.

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