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Behaviour of enaminomalonates and enamidomalonates under various reductive conditions: a novel synthetic approach to *N*-acetyl-*N*-aryl β-amino acids

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Abstract

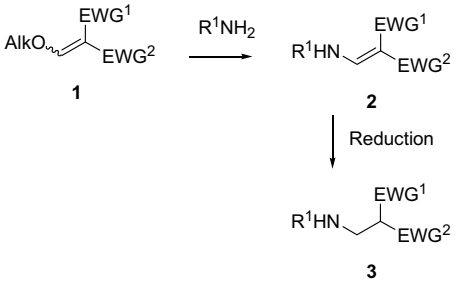
The behaviour of enaminomalonates and their deprotection to amines under various reductive conditions is described. A new synthetic approach to *N*-aryl-*N*-acetyl-β-amino acids using heterogeneous catalytic hydrogenation has been discovered.

Keywords: Reduction; β-Amino acid; Enaminoester; Deprotection

Recently, racemic and enantiomerically enriched β-amino acids and their derivatives have gained much attention within the chemical community for being versatile tools for synthetic chemists.[1] Enantiomerically enriched β-amino carboxylic acids occur in natural substances such as alkaloids and antibiotics.[2] Both the free form of these β-amino carboxylic acids and their derivatives show interesting pharmacological effects and can also be employed in the synthesis of modified peptides.[1,2]

Alkoxymethylene compounds **1** (Scheme 1) are tricentric electrophilic enol ethers suitable for the synthesis of various types of heterocycle.[3]

The reaction of amines with alkoxymethylene compounds **1** is used for the protection of the amino group, especially in amino sugar chemistry.[4,5] Replacement of the alkoxy group with amines yields aminomethylene derivatives **2**, which are potential precursors of β-amino acids **3** (Scheme 1). Such a chemoselective reduction of the double bond in **2** would provide a general synthetic route to β-amino acid derivatives from the easily available alkoxymethylene compounds **1** in two simple steps. Herein



Scheme 1.

are presented results from screening various conditions for the reduction of enaminonitriles and enaminoesters **2**.

There are a few examples reported in the literature for the selective reduction of double bonds as in specific systems **2**. These involve high pressure catalytic hydrogenation (1000 psi) or a combination of borane and sodium borohydride reduction.[6–8] Model studies were carried out on the easily synthesized aminomalonate system **2a**, available from aniline **4** and enol ether **1a** (Alk = Me, Et, R^1 = Ph, $EWG^1 = EWG^2$ = COOMe, Scheme 2).[9]

$NaBH_4/I_2$ was employed as a reductive system on substrate **2a**, but only produced an equimolar mixture of aniline **4** and dimethylmethylmalonate **5** (Scheme 2).[10]

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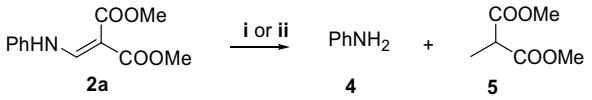


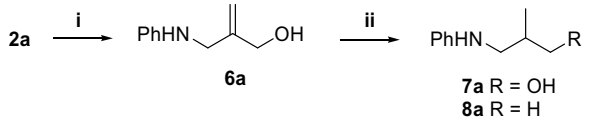
Scheme 2. Reagents and conditions: (i) $NaBH_4$, I_2, THF, 0 °C, 30 min, 60%; (ii) Pd/C, H_2, 4 h, rt, 73%.

Decreasing the reaction temperature to −50 °C reduced the reaction rate but gave the same products.

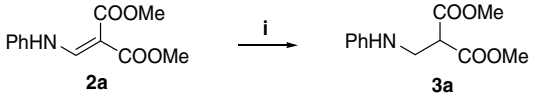
Our subsequent approach employed catalytic hydrogenation. We screened various conditions, modifying the usual parameters (temperature, pressure, reaction time, and type of catalyst). The major products from this screen were again aniline **4** and dimethylmethylmalonate **5** (Scheme 2). However, these conditions can be useful for the deprotection of amines protected as alkylidenemalonates. Alternatively, the reduction system can be used for the indirect methylation of malonates using aniline, orthoformate and a reducing reagent.

Next, we turned our attention to the use of complex hydrides. Reduction with sodium borohydride under various conditions failed to produce the desired product **3a**. Even employing $Na(CN)BH_3$ as previously reported did not solve the problem, as **2a** was inert under various conditions (AcOH, rt or MeOH, reflux). These results prompted us to activate substrate **2a** with Lewis acids. Unfortunately, such modifications led to very complex reaction mixtures. Therefore, in a subsequent screen, we turned our attention towards more reactive complex hydrides. Using a large excess of lithium aluminium hydride in the reduction of **2a** led, as expected, to over reduction producing mainly the unsaturated amino alcohol **6a**. This structure was confirmed by analytical methods, and further transformation to **7a** and **8a**, via hydrogenation using a standard catalyst (Pd/C, Scheme 3). Interestingly, under very mild conditions, the saturated amino alcohol **7a** as well as amine **8a** was isolated.

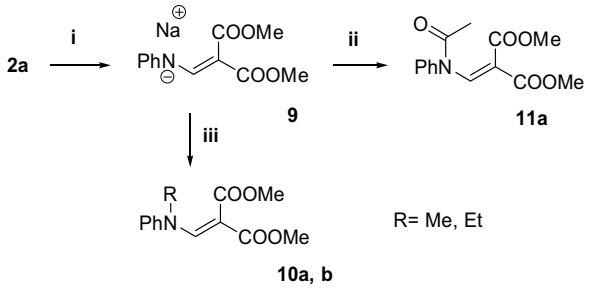
These results prompted us to modify the reaction conditions to synthesize the desired amino ester. By changing the reaction parameters (the amount of LAH, reaction time) an 18% yield of **3a** was isolated from the complex reaction mixture (Scheme 4). This low yield led to further reduction systems being investigated.



Scheme 3. Reagents and conditions: (i) LAH (excess), THF, rt, 24 h, 52%; (ii) H_2, Pd/C, rt, 24 h, **7a** 30%, **8a** 24%.



Scheme 4. Reagents and conditions: (i) LAH, THF, 0 °C, 1 h, 18%.



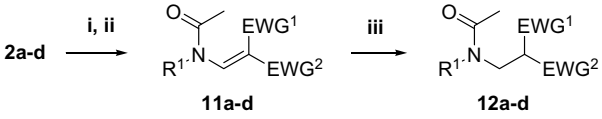
Scheme 5. Reagents and conditions: (i) Na, xylene, reflux, 24 h, 95%; (ii) acetic anhydride, DMF, rt, 0.5 h, 72%; (iii) RBr, THF, rt, 45–60%.

In the next step, we turned our attention to reduction using metals under various conditions. The chemoselective reduction of conjugated double bonds has been reported with elemental magnesium (Mg, MeOH, rt) or with zinc (Zn, AcOH, rt).[11] However, the application of such reductive agents to **2a** led to very complex reaction mixtures.

The use of sodium in xylene produced the sodium salt **9** as the major product (95% yield). This structure was confirmed by the subsequent N-alkylation and acylation of **9a** leading to the known compounds **10a** and **11a** (Scheme 5).[12]

The results described so far show the complexity of enaminomalonates as substrates for high yielding chemoselective reduction of their double bond. We therefore decided to use the more stable N-acylated **11a** for further study.[13] This would produce the more stable N-acylated reduced product **12a** (Scheme 6). Using enamidomalonate **11a** we searched for suitable reducing conditions. Catalytic hydrogenation of **11a** performed under very mild reaction conditions produced the desired N-acylated β-amino ester **12a** in excellent yield (Scheme 6, Table 1, entry **2a**).

Consequently, this transformation was generalized for more complex substrates. Thus, enamidomalonates **11b–d** were prepared under mild conditions in good yields using sodium hydride for the generation of the sodium salt followed by acylation (Scheme 6, Table 1).[14] Chemoselective catalytic reduction of enamidomalonates **11b–d** under mild reaction conditions produced the β-amino esters

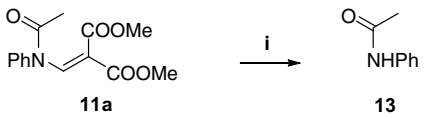


Scheme 6. Reagents and conditions: (i) NaH, THF; (ii) Ac_2O, 0.5 h, reflux; (iii) H_2, Pd/C, rt, 0.5–3 h.

Table 1
Reduction of enamidomalonates with H_2/Pd/C

Entry	EWG^1	EWG^2	R^1	Yield **11**	Yield **12**
2a	COOMe	COOMe	Ph	97	91
2b	COOMe	CN	Ph	66[a,b]	42
2c	COOMe	COOMe	2-Naphthyl	91	96
2d	COOMe	COOMe	4-Tolyl	92	94

[a] Employing Na in xylene for the generation of the Na-salt.
[b] *Z*-Isomer only.



Scheme 7. Reagents and conditions: (i) EtMgBr, THF, 0 °C→rt, 16 h, 82%.

12b–d. Our synthetic approach tolerated different aryl substituents on nitrogen. Moreover, it was possible to reduce the *N*-acetyl substrate **11** with two different electron-withdrawing substituents. Starting with *Z*-configured substrates **11b** we obtained amino ester **12b** in racemic form. This result is very promising for the development of an asymmetric version of the reduction. The procedure is very attractive due to its ease (room temperature, only slightly higher pressure, short reaction time), simple work up and good to excellent yields.[15]

Finally, we investigated the reactivity of **11a** towards nucleophiles for the selective deprotection of N-acylated amines protected with alkylidenemalonates. Chemoselective deprotection of **11a** was achieved using ethylmagnesium bromide in a very good yield under mild reaction conditions, yielding *N*-acetylaniline **13** (Scheme 7).

In conclusion, the behaviour of aminomalonates and amidomalonates under various reductive conditions has been examined. A new approach for the deprotection of amines protected with an alkylidene malonate group, and a new synthetic approach to N-acylated β-amino esters are described. Our current efforts in this area are directed towards the extension of the strategy to an asymmetric reduction using chiral catalysts and/or using chiral substrates.

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15. *Typical procedure*: **11a** (1.8 mmol, 500 mg) was dissolved in MeOH (15 mL) and 10% Pd/C (100 mg) was added. The resulting suspension was vigorously stirred in a Paar-apparatus (rt, 2.5 atm) until complete consumption of the starting material (TLC monitoring, typically 2 h). The catalyst was filtered off and washed with MeOH (10 mL). The filtrate was concentrated in vacuo and dried to produce the title compound **12a** (460 mg, 91%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.83 (s, 3H, CH_3CO), 3.66 (s, 6H, CH_3O), 3.81 (t, 1H, $J = 7.6$ Hz, CHCH$_2$), 4.26 (d, 2H, $J = 7.6$ Hz, CHCH_2), 7.14–7.18 (m, 2H, *H*-Ph), 7.30–7.43 (m, 3H, *H*-Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.6 (*C*H$_3$CO), 48.1 (*C*HCH$_2$), 50.0 (CH*C*H$_2$), 52.5 (2 × *C*H$_3$O), 127.8, 128.0, 129.6, 142.4 (*C*-Ar), 167.9 (2 × *C*=O), 170.7 (*C*=O).