Enamine-Based Domino Strategy for C-Acylation/Deacetylation of Acetoacetamides: A Practical Synthesis of β-Keto Amides

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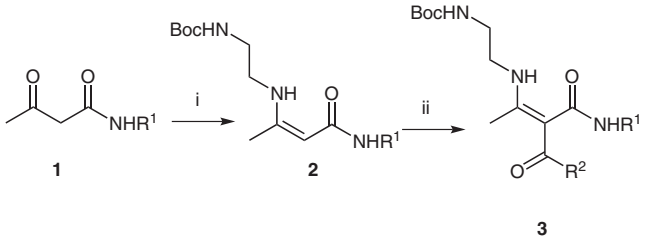
Abstract: A practical three-step route for C-acylation/deacetylation of acetoacetamides is described. Initial enamination of the acetoacetamides with Boc-monoprotected ethylenediamine provides β-enamino amides, which are acylated at the α-carbon with excellent selectivity. The C-acylated derivatives undergo domino fragmentation in acidic media to give the corresponding β-keto amides accompanied by 2-methyl-4,5-dihydro-1*H*-imidazole.

Key words: β-keto amide, enaminone, C-acylation, domino reaction, 1,3-dicarbonyl

β-Keto amides are widely used in the synthesis of various heterocyclic compounds.[1] In addition to that, many biologically active compounds contain β-keto amide fragments in their structure.[2] As a consequence, considerable efforts have been directed towards the development of synthetic methodologies giving access to this class of compounds. Depending on the retrosynthetic disconnection, the methods for β-keto amide synthesis can be divided into three main categories: a) acylation of amide enolates[3] or their synthetic equivalents,[4] including asymmetric acylations,[5] b) addition of ketone enolates to isocyanates[6] or Passerini condensation followed by reduction,[7] and, c) coupling of amines and β-keto acids[8] or their synthetic equivalents, such as β-keto esters,[9] β-keto thioesters,[10] 2,2-difluoro-4-alkoxy-1,3,2-dioxaborinanes,[11] ketene dimers[12] and acylketenes obtained in situ from 1,3-dioxin-4-ones[13] or acylated Meldrum's acids.[2b,c,14]

C-Acylation/deacetylation is a well-established approach for the synthesis of β-diketones and β-keto esters from acetylacetone and acetoacetic esters, respectively,[15] but to the best of the author's knowledge it has never been applied to acetoacetamides, despite their general availability. The methodology presented in this letter may be regarded as an enamine-assisted variation of the C-acylation/deacetylation approach, which applied to acetoacetamides turns them into synthetic equivalents of amide enolates. The idea for the present investigation originated from two earlier observations; the selective and high-yielding α-C-acylation of β-enamino amides[16] and the retro-Mannich reactions of some 1,1-disubstituted tetrahydroisoquinolines.[17] Putting these two pieces of information together, it was envisaged that enamination of acetoacetamides with monoprotected ethylenediamine would both provide excellent starting material for α-C-acylation and set the scene for a domino-like sequence of intramolecular Michael addition and retro-Mannich fragmentation. The required Boc-monoprotected ethylenediamine was easily prepared in 75% yield by reacting di-*tert*-butyl dicarbonate with excess of ethylenediamine.[18] This material was then reacted with acetoacetamides **1** (Scheme 1, i) to provide the corresponding β-enamino amides **2** in quantitative yields.[19] The acylation of the enamino amides **2** with acid chlorides (Scheme 1, ii, Table 1) was carried out in the presence of equimolar amount of triethylamine and was greatly facilitated by DMAP catalysis (0.2 equiv catalyst). The reactions were carried out in dichloromethane for one hour at room temperature and the C-acylated products **3** were obtained in high yields (75–95%).[20]



Scheme 1 *Reagents and conditions*: (i) $BocNHCH_2CH_2NH_2$, Na_2SO_4, CH_2Cl_2 or MeOH, 24 h, r.t.; (ii) DMAP (0.2 equiv), Et_3N, R^2COCl, CH_2Cl_2, 1 h, r.t.

The final stage of the synthesis was a Boc-deprotection of **3** with TFA, which triggered the expected domino sequence of intramolecular Michael addition followed by retro-Mannich fragmentation (Scheme 2). Thus, the β-keto amides **6** were obtained in excellent yields with accompanying formation of 2-methyl-4,5-dihydro-1*H*-imidazole (**5**).[21] Although this co-product is of no practical interest here, the approach may prove useful for the preparation of other 2-substituted dihydroimidazoles, considering the mild reaction conditions. The intermediate **4** was not isolated. It appears to be rather unstable and at this stage it is not clear whether the domino process takes place in the acidic solution or during the aqueous workup.

In conclusion, a practical and straightforward synthesis of β-keto amides has been disclosed. It does not require an inert atmosphere[22] and in most cases can be done without

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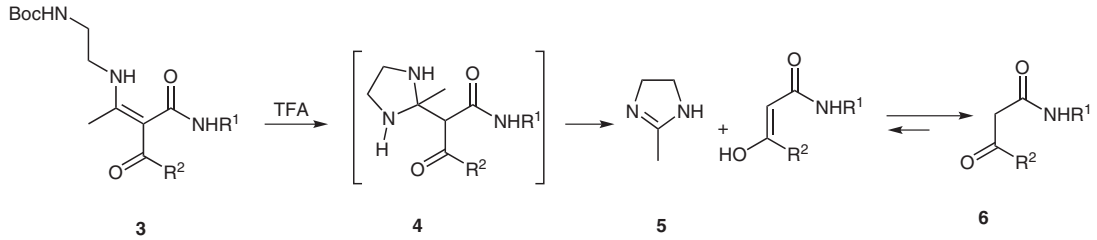

3 4 5 6

Scheme 2

Table 1 Isolated Yields of Compounds **3** and **6** Obtained According to Scheme 1 and Scheme 2

Compd	R^1	R^2	Yield (%)	
			3	**6**
a	Ph	*i*-Pr	77	88
b	Ph	*i*-Bu	90	93
c	Ph	Bn	75	90
d	Ph	Ph	95	95
e	CH_2CH_2Ph	*i*-Bu	89	96
f	CH_2CH_2Ph	Bn	75	90
g	CH_2CH_2Ph	Ph	93	97
h	H	*n*-C_9H_{19}	85	95
i	H	CH_2CH_2Ph	80	80

chromatographic purification. Work to extend this methodology to other 1,3-dicarbonyl compounds is currently in progress and the results will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **Preparation of β-Enamino Amides 2**: The corresponding acetoacetamide **1** (5 mmol) was added to a solution of Boc-monoprotected ethylenediamine (5 mmol) in CH_2Cl_2 (20 mL) or MeOH (20 mL) for acetoacetamide **1h** (**1**, R^1 = H) and the reaction mixture was stirred over anhyd Na_2SO_4 for 24 h at r.t. After that, the sulfate was filtered off and the solvent was removed by distillation. The residue was triturated with small amount of Et_2O to give practically clean β-enamino amide in nearly quantitative yield (93–98%). Compound **2a** (**2**, R^1 = Ph) has moderate solubility in CH_2Cl_2 and crystallizes out of the reaction mixture, so special care must be taken to wash it thoroughly off the drying agent. The β-enamino amides **2** are air-stable and can be stored safely at r.t., but they easily decompose on silica gel.
(20) **Preparation of α-Acyl-β-enamino Amides 3; General Procedure**: The corresponding acid chloride (1 mmol) was slowly added to a magnetically stirred solution of enamino amide **2** (1 mmol), DMAP (0.2 mmol, 25 mg) and Et_3N (1 mmol, 0.14 mL) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 1 h at r.t. and after that was transferred to a separating funnel with additional 20 mL of CH_2Cl_2, where it was washed with 5% aq solution of AcOH (15 mL) and then with sat. aq $NaHCO_3$ (15 mL). The organic phase was dried over Na_2SO_4 and the solvent was distilled off. The residue crystallized upon trituration with Et_2O or Et_2O–PE (1:1) to give the corresponding product **3** in 50–90% yield. Additional 10–30% were isolated from the ethereal washings after column chromatography on silica gel with Et_2O as the eluent [increasing polarity to Et_2O–MeOH (10:1) for products **3** with R^1 = H].
(21) **Preparation of β-Keto Amides 6; General Procedure**: The corresponding intermediate **3** (200 mg) was dissolved in TFA (2 mL), the solution was stirred for 40 min at r.t. and the reaction was quenched with aq solution of MeCOONa (3 mol/L, 20 mL). The resulting mixture was stirred for 20 min at r.t. and then extracted with CH_2Cl_2 [3 × 20 mL (5 × 20 mL for **6h** and 10 × 20 mL for **6c** and **6i**)]. In the case of **6i** the aqueous phase was saturated with NaCl prior to extraction. The combined organic layers were washed with sat. aq $NaHCO_3$ (15 mL) and dried over Na_2SO_4. The solvent was distilled off to afford practically clean β-keto amides. In some cases enol tautomer was registered immediately after isolation, but it gradually converted to the keto form.
(22) All reactions were carried out in untreated CH_2Cl_2 and open to air.