Direct, facile synthesis of *N*-acyl-α-amino amides from α-keto esters and ammonia†

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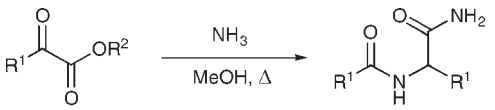
Received (in College Park, MD, USA) 16th May 2008, Accepted 17th June 2008
First published as an Advance Article on the web 23rd July 2008
DOI: 10.1039/b808302a

***N*-Acyl-α-amino amides were prepared, without the necessity of chromatographic purification, in a single step by heating the corresponding α-keto ester in methanolic ammonia.**

Amines are an important class of organic compounds with widespread applications in the pharmaceutical, agrochemical and fine chemical industries.[1] Amino acids and their derivatives, in particular non-natural variants, form an important subset of amines that are in demand due to their varied use in biological and medicinal chemistry.[2,3] Consequently, any new methodology that allows for the rapid, cost-effective synthesis of these compounds from readily available precursors would be desirable.

As part of an ongoing study into *N*-unsubstituted imines,[4] we found that α-keto esters (**1**),[5] when reacted with ammonia, readily formed *N*-acyl-α-amino amides **2** (eqn (1)).[6,7] Compound **2** is an important starting material for the synthesis of a variety of heterocycles including oxazoles,[8] thiazoles,[9] oxazolones[10] and imidazolones.[11]



1 **2** (1)

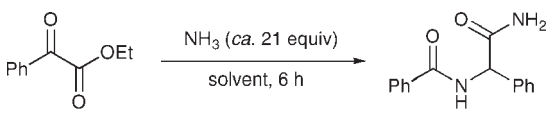
We initially optimized the formation of **2** (R^1 = Ph, R^2 = Et) by varying several reaction parameters (Table 1).[12] The results indicated that the solvent had a profound effect on the overall isolated yield, with methanol proving to be the solvent of choice (entries 1–3). In addition, elevated temperatures (entries 4 and 5) and an excess of ammonia were required to achieve satisfactory isolated yields within a reasonable period of time. We determined that the only major by-product of the reaction mixture was the corresponding α-keto amide (formed through initial aminolysis of **1a**).

The optimal reaction conditions of reacting **1** with ammonia (*ca.* 21 equiv.) in methanol (0.33 M) at 60 °C for 6 h were subsequently employed when examining the substrate scope of the reaction (Table 2, *vide infra*).§ The results show that a variety of α-keto esters (**1**) successfully reacted under the aforementioned conditions to afford the desired *N*-acyl-α-amino amides **2** in high yields. In particular, electron rich (entry 5), electron deficient (entries 6 and 7) and *ortho*-substituted (entries 2–4) aromatic α-keto esters **1** (R^1 = aryl) were suitable substrates, and furnished **2** in good yields. The reaction conditions were also tolerant of functional groups such as nitro (entry 6) and halides (entries 4 and 7). In addition, a heteroaromatic variant of **1** also successfully reacted to provide **2k** in excellent yield (entry 11). A single crystal X-ray structure of one of the aromatic *N*-acyl-α-amino amide products (**2a**) was also obtained (Fig. 1).[13]

Aliphatic α-keto esters, however, reacted more sluggishly under the conditions listed above. However, elevating the reaction temperature to 80 °C for 12 h allowed the desired products **2l–m** to be isolated in good yields (entries 12–14). It should be noted that all the *N*-acyl-α-amino amide products (**2**) were obtained as solids through direct precipitation or crystallization from the crude reaction mixture, and did not require any further purification (*e.g.* column chromatography or preparative TLC).

We next sought to determine whether the *N*-acyl-α-amino amides could be hydrolyzed to the corresponding α-amino acids. Towards that end, when compound **2a** was heated to reflux in concentrated hydrochloric acid for 12 h, 2-phenylglycine **3** was obtained in 94% isolated yield after ion-exchange chromatography (eqn (2)). We anticipate that other unnatural

Table 1 Optimization studies on the formation of *N*-acyl-α-amino amide **2a**



1a **2a**

Entry	Temperature/°C	Solvent[a]	Yield of **2a** (%)[b]
1	60	MeOH	90
2	60	$PhCH_3$	<10
3	60	THF	24
4	20	MeOH	<10
5	90	MeOH	84

[a] 0.33 M **1a**. [b] Isolated yield.

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† Electronic supplementary information (ESI) available: Optimization studies, full synthetic and characterization data, and NMR spectra of **2**. CCDC reference numbers 688365. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/b808302a

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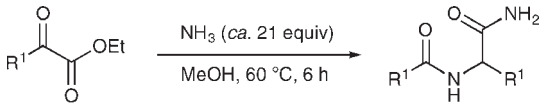
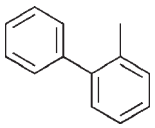
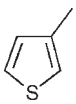
Table 2 Synthesis of *N*-acyl-α-amino amides **2** from α-keto esters

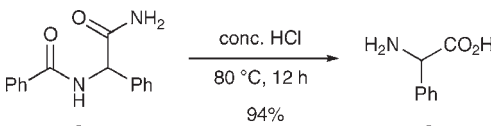


1 **2**

Entry	R^1	Yield (%)[a]
1	Ph (**1a**)	90 (**2a**)
2	2-$CH_3C_6H_4$ (**1b**)	84 (**2b**)
3	 (**1c**)	88 (**2c**)
4	2-BrC_6H_4 (**1d**)	84 (**2d**)
5	3-$MeOC_6H_4$ (**1e**)	86 (**2e**)
6	3-$O_2NC_6H_4$ (**1f**)	81 (**2f**)
7	4-FC_6H_4 (**1g**)	92 (**2g**)
8	4-$MeOC_6H_4$ (**1h**)	95 (**2h**)
9	1-Naphthyl (**1i**)	91 (**2i**)
10	2-Naphthyl (**1j**)	91 (**2j**)
11	 (**1k**)	93 (**2k**)
12	CH_3 (**1l**)	80 (**2l**)[b]
13	$(CH_3)_2CH$ (**1m**)	75 (**2m**)[b]
14	$PhCH_2$ (**1n**)	80 (**2n**)[b]

[a] Isolated yield. [b] Reaction conducted at 80 °C for 12 h.

α-amino acids could be synthesized from **2** under analogous conditions.



2a **3** (2)

A plausible mechanism for the reaction methodology under current development is shown in Scheme 1, and is based upon a proposal originally put forth by Shive and Shive.[14]

We briefly examined the plausibility of the proposed mechanism by reacting **1a** with deuterated ammonia in deuterated methanol under otherwise standard conditions (eqn (3)). It was determined that there was >98% deuterium incorporation at the α-position of **2o**. We attribute the lower deuterium

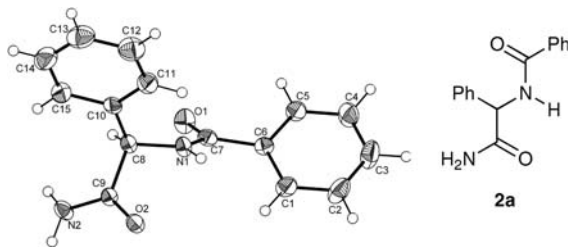
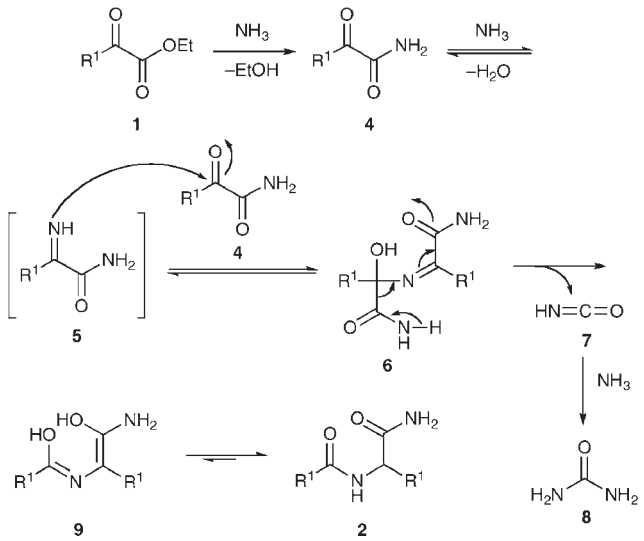
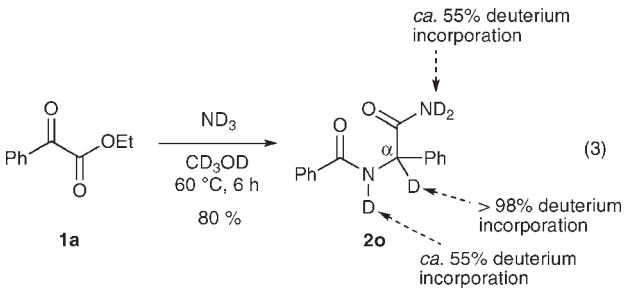


Fig. 1 X-ray crystal structure of **2a**.



Scheme 1 Proposed overview of the mechanism for the formation of **2**.

incorporation at the amide protons to post-isolation deuterium–hydrogen exchange with adventitious water in the NMR solvent (DMSO-d_6). These results, however, support the formation of enol intermediate **9**, with the source of the proton being ammonia and/or methanol. In addition, further support for the proposed mechanism comes from the ^{1}H NMR analysis of the crude reaction mixture upon reaction of **1a** under the standard conditions which showed the presence of a trace amount of urea (**8**).[15] We attribute the formation of urea to nucleophilic attack of ammonia on liberated isocyanate (**7**) (Scheme 1). Further studies to elucidate the details of the mechanism are ongoing.



1a **2o** (3)

In conclusion, we have developed a methodology for the direct and facile synthesis of a variety of *N*-acyl-α-amino amides in one step from α-keto esters. The desired products are obtained in good to excellent yields through simple precipitation or recrystallization from the crude reaction mixture, and do not require any further purification. Preliminary work towards deducing the mechanism of this transformation was also presented.

This work was supported through funding from NSERC of Canada and Kanata Chemical Technologies. We thank Bhartesh Dhudshia and Jennifer Scott for preparation of certain α-keto esters.

Notes and references

§ **General experimental procedure for the synthesis of *N*-acyl-α-amino amides:** *CAUTION: the procedure described below generates pressure in a closed reaction vessel. The reaction vessel should be placed behind a blast shield in a well-ventilated fume hood.*
To a solution of ammonia in methanol (*ca.* 7 M in MeOH, 3.0 mL, *ca.* 21 equiv.) in a Swagelock® 50 mL stainless steel cylinder or an Ace® pressure tube was added the α-keto ester (1.00 mmol). The cylinder (or tube) was sealed and heated in an oil bath at 60 °C or 80 °C for 6 h or 12 h. The cylinder (or tube) was then removed, was allowed to cool to room temperature (1 h), and then cooled further in a −40 °C bath. The Swagelock® cylinder (or pressure tube) was opened and the contents were transferred to a small Erlenmeyer flask (50 mL). A steady stream of air was blown over the reaction mixture until some precipitation was observed. The reaction mixture was then heated slightly to redissolve all solid matter, and allowed to stand at room temperature for 2 h. The precipitated product was filtered off through a sintered glass funnel, and washed with ice-cold methanol (*ca.* 5 mL).

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12 See ESI† for detailed optimization studies.
13 *Crystal data*, **2a**: $C_{15}H_{14}N_2O_2$, M = 254.28, monoclinic, space group $C2/c$, a = 18.101(4) Å, β = 7.1667(14) Å, c = 20.677(4) Å, β = 101.16(3)°, V = 2631.6(9) Å^3, Z = 8, T = 293(2) K, μ(Mo-Kα) = 0.087 mm^{-1}, 7631 reflections collected, 2245 unique (R_{int} = 0.0527), F^2 refinement, $R1$ = 0.0446, w$R2$ = 0.1161, (1649 reflections, $I > 2\sigma(I)$). Goodness-of-fit = 1.067. Data were collected on a Nonius Kappa CCD instrument and solutions performed using the SHELXTL 5.03 Program Library, Siemens Analytical Instrument Division, Madison, WI, USA, 1997. CCDC 688365.
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