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One-pot synthesis of α-acyloxyaminoamides via nitrones as imine surrogates in the Ugi MCR

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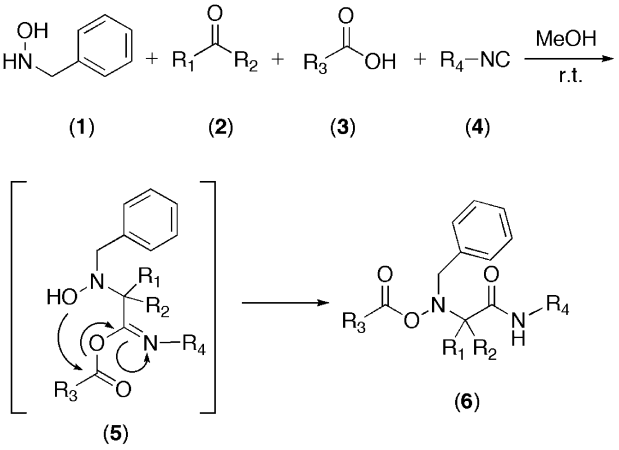
Abstract—α-acyloxyaminoamides can be prepared, with yields ranging from fair to very good (up to 89%), through an Ugi four component reaction by mixing a carbonyl component, a carboxylic acid, an isocyanide and an *N*-alkylated hydroxylamine in methanol. Preformed nitrones furnish the same final compounds with comparable yields.

The success of multicomponent condensations in organic synthesis during the last few years has increased the interest for novel reactions or modifications of old ones. Such modifications can include the use of polyfunctional building blocks, that can be further elaborated after the multicomponent condensation, or the employment of non-classical starting units. For this purpose, our group has recently published a modification of the Ugi four component reaction employing *O*-protected and unprotected hydroxylamines as amine components to prepare hydroxamic acid derivatives.[1] The intrinsic advantages of multicomponent reactions in comparison to classical linear synthesis—that are high convergence, versatility, ease of assemblage and purification and complexity of the final products—make this synthetic strategy highly attractive to prepare combinatorial libraries of hydroxamic acids, compounds known for their different pharmacological applications.[2]

Within the same research project, we wish now to report the results of our investigations on the employment of *N*-monoalkylated hydroxylamines[3] as amine components in the Ugi reaction. Disubstituted amines have already been used in Ugi condensations,[4] and we recently reported a stereoselective intramolecular version of this reaction to prepare α-aminoacid derivatives with very high ees.[5]

In a first experiment, we mixed equimolar amounts of *N*-benzylhydroxylamine **1**, isovaleric aldehyde (**2**, $R_1 = i$-Bu, $R_2 = H$), phenylacetic acid (**3**, $R_3 = Bn$) and *n*-butyl isocyanide (**4**, $R_4 = n$-Bu) in methanol and after 48 h, we isolated a compound incorporating all four building blocks in its structure and that was found to be α-acyloxyaminoamide **6**[6] (Scheme 1). The formation of **6** can be rationalised assuming the initial condensation of the aldehyde with *N*-benzylhydroxylamine to give the corresponding nitrone, followed by the addition of the isocyanide and the carboxylic acid with the formation of intermediate **5**, that can rearrange via migration of the acyl group onto the oxygen of the



Scheme 1. General scheme for the Ugi condensation between *N*-benzylhydroxylamine, carbonyl derivatives, carboxylic acids and isocyanides.

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hydroxylamine, giving the final compound **6** (Scheme 1). To confirm this hypothesis, we also preformed and isolated the nitrone, and then reacted it with the same isocyanide and carboxylic acid, obtaining also in this case compound **6**, with comparable yield after only 24 h.

Although nitrones have been extensively employed in organic synthesis, for example, in nucleophilic additions[7] or dipolar cycloadditions,[8] it is noteworthy that they have never been used in Ugi multicomponent reactions.

Having in mind, our previous experience on *O*-protected hydroxylamines,[1] where the presence of a Lewis acid was found crucial for the reaction to occur, we performed also the reaction in tetrahydrofuran in the presence of 1 equiv of etherated zinc chloride. However, while in methanol compound **6** was isolated in 70% yield after chromatographic purification, in tetrahydrofuran the recovery was only 45%, probably because nitrones are more reactive than oximes and activation by a Lewis acid facilitates formation of side products as well.

In order to prove the versatility of this novel reaction, we synthesised a small collection of compounds by reacting equimolar amounts of various aldehydes, isocyanides and carboxylic acids with *N*-benzyl hydroxylamine (0.9 equiv referred to the other reagents) in methanol. To our delight we found that the desired product could be isolated in all cases, with yields ranging from fair to very good, as reported in Table 1 (entries a–k).

Only the condensations with aromatic aldehydes did not give any product and the resulting nitrones remained unreacted (entries l–n). These latter reactions were performed also in tetrahydrofuran with a Lewis acid, but no improvement was found.

We also investigated the reaction with ketones as carbonyl component; among a panel of commercially available ketones, we observed that only aliphatic methyl ketones gave the expected α-acyloxyamino-α,α-disubstituted amide (**6**, $R_2 \neq H$) to some extent (Table 1, entries o–u), while other ketones such as 3-pentanone, acetophenone or cyclohexanone did not react at all (entries v–x). Although it has been reported that nitrone formation is difficult with hindered ketones,[9] we think that the crucial step is not the formation of the nitrone itself but the subsequent condensation with the isocyanide and the carboxylic acid; we observed in fact that pre-formed nitrones did not give better conversions and that the reaction with cyclohexanone did not proceed at all, although the nitrone was formed smoothly.

To the best of our knowledge, α-acyloxyaminoamides **6** have never been employed in any biological applications, while the parent α-hydroxylaminoamides have been used, for example, as protease inhibitors[10,11] or anticonvulsants:[12] collections of such molecules can be obtained with our multicomponent approach in a very straightforward way and subsequent removal of the acyl group from compounds **6**. To this end, we treated some representative α-acyloxyaminoamides **6q–s** with 1.1 equiv of

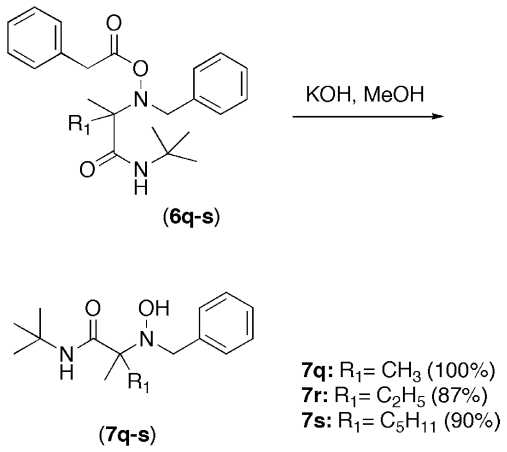
Table 1. Yields are referred to isolated products purified by flash chromatography

	Carbonyl component **2**	Acid **3**	Isocyanide **4**	Yield of **6** (%)
a	Isovaleraldehyde	Phenylacetic	*n*-Butyl	70
b	Isovaleraldehyde	Phenylacetic	*tert*-Butyl	86
c	Isovaleraldehyde	Benzoic	Ethoxycarbonylmethyl	74
d	Isovaleraldehyde	Benzoic	*tert*-Butyl	86
e	Isovaleraldehyde	N-Boc-Ala-OH	*tert*-Butyl	89[a]
f	Isovaleraldehyde	N-Boc-Val-OH	*tert*-Butyl	85[a]
g	Isovaleraldehyde	N-Cbz-Gly-OH	*n*-Butyl	61
h	Phenylacetaldehyde	Acetic	Benzyl	82
i	Propionaldehyde	N-Cbz-Gly-OH	*tert*-Butyl	62
j	Propionaldehyde	Phenylacetic	*tert*-Butyl	67
k	Propionaldehyde	Acetic	Ethoxycarbonylmethyl	73
l	Benzaldehyde	Phenylacetic	*n*-Butyl	—[b]
m	4-Chlorobenzaldehyde	Phenylacetic	*n*-Butyl	—[b]
n	4-Methoxybenzaldehyde	Phenylacetic	*n*-Butyl	—[b]
o	Acetone	Benzoic	*n*-Butyl	65
p	Acetone	Phenylacetic	Ethoxycarbonylmethyl	71
q	Acetone	Phenylacetic	*tert*-Butyl	65
r	2-Butanone	Phenylacetic	*tert*-Butyl	56
s	2-Heptanone	Phenylacetic	*tert*-Butyl	33
t	4-Methyl-2-pentanone	Phenylacetic	*tert*-Butyl	<5
u	5-Hexen-2-one	Phenylacetic	*tert*-Butyl	59
v	3-Pentanone	Phenylacetic	*tert*-Butyl	—[b]
w	Acetophenone	Phenylacetic	*tert*-Butyl	—[b]
x	Cyclohexanone	Phenylacetic	*tert*-Butyl	—[b]

Typical conditions were 0.40 mmol of hydroxylamine and 0.44 mmol of carbonyl compound dissolved in dry methanol (1 mL) at room temperature, followed by the addition of 0.44 mmol of acid and isocyanide after 30 min; the mixture was left stirring at room temperature for 2–5 days, then the solvent evaporated and the crude purified by flash chromatography. All compounds were fully characterised by NMR and LC/MS or GC/MS.

[a] These compounds were obtained as a 1:1 diastereomeric mixture.

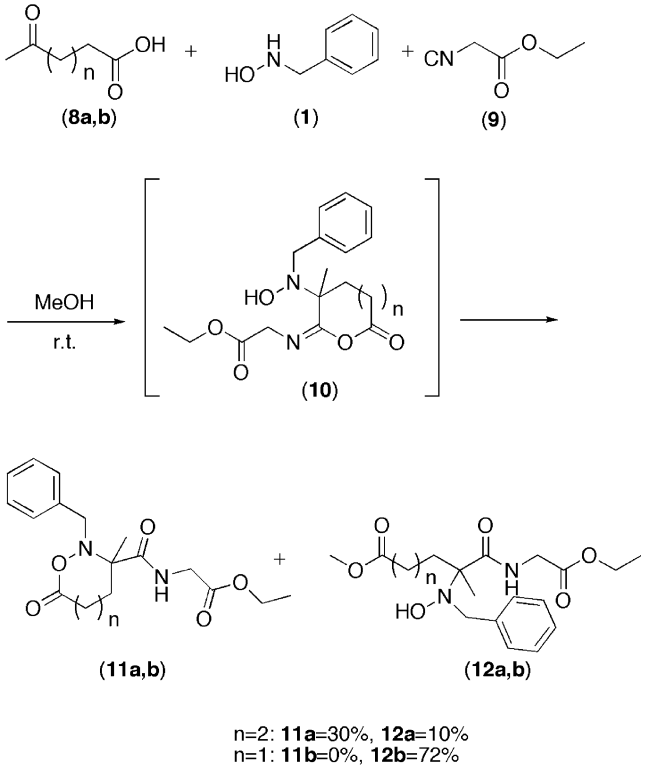
[b] See text.



Scheme 2. Hydrolysis of the acyl group was achieved under mild conditions with KOH/MeOH.

potassium hydroxide in a 0.1 M methanolic solution at room temperature and obtained the corresponding *N*-benzyl-α,α-disubstituted-α-hydroxylaminoamides **7q–s** in high yields (Scheme 2).

When we explored the intramolecular version of this reaction condensing bifunctional ketones 4-acetylbutyric acid (**8a**, $n = 2$) and levulinic acid (**8b**, $n = 1$) with *N*-benzylhydroxylamine **1** and ethyl isocyanoacetate **9**, we found that, when **8a** was employed, the desired oxazepinone **11a** was isolated in moderate yield, together with another compound, slightly less polar in TLC, that was identified to be the corresponding acyclic α-hydroxylaminoamide **12a**, incorporating one molecule of methanol at the carboxylic function. On the other hand, when **8b** was employed instead, only the methyl ester **12b** could be isolated in good yield (Scheme 3).



Scheme 3. Intramolecular reaction with ketoacids as bifunctional components.

Apparently, due to the cyclic nature of intermediates **10**, the nucleophilic attack by a molecule of methanol becomes competitive with the intramolecular migration of the acyl group, while this is not observed for intermolecular reactions, where acyclic intermediates (such as **5** of Scheme 1) have a higher degree of freedom, or when a primary amine is used instead of **1**.[13]

In conclusion, in this letter we have reported the first examples of Ugi four component condensation employing *N*-alkylated hydroxylamines as secondary amine components and we have demonstrated that this reaction follows an unusual path, with the acyl group migrating onto the hydroxylamine oxygen, giving α-acyloxyaminoamides. We have also tested the versatility of this multicomponent condensation with a number of different reactants; furthermore, we proved that these compounds can be transformed smoothly into polysubstituted α-hydroxylaminoamides, compounds that find pharmacological applications in various fields. We will report further investigations in this field in due course.

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References and notes

1. Basso, A.; Banfi, L.; Guanti, G.; Riva, R.; Riu, A. *Tetrahedron Lett.* **2004**, *45*, 6109; For former examples of reactions of hydroxylamines with isocyanides and aldehydes see: (a) Zinner, G.; Moderhack, D.; Kliegel, W. *Chem. Ber.* **1969**, *102*, 2536; (b) Moderhack, D. *Liebigs Ann. Chem.* **1973**, 359; (c) Zinner, G.; Moderhack, D.; Hantelmann, O.; Bock, W. *Chem. Ber.* **1974**, *107*, 2947.
2. Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735, MD.
3. See for example: Trost, B. M.; Fleming, I. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 6, p 111.
4. See for example: Bonne, D.; Dekhane, M.; Zhu, J. P. *Org. Lett.* **2004**, *6*, 4771.
5. (a) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587; (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575.
6. Experimental data: ^{1}H NMR: 0.8–1.0 [9H, m]; 1.2–1.9 [7H, m]; 3.0–3.2 [2H, m]; 3.38 [2H, s]; 3.53 [1H, dd, *J* 8, 5]; 3.97 [1H, d, *J* 13]; 4.08 [1H, d, *J* 13]; 7.0–7.10 [2H, m]; 7.15–7.40 [9H, m]. ^{13}C NMR: 13.7 [CH_3]; 20.0 [CH_2]; 22.1 [CH_3]; 23.2 [CH_3]; 25.7 [CH]; 31.5 [CH_2]; 37.1 [CH_2]; 38.8 [CH_2]; 39.6 [CH_2]; 60.0 [CH_2]; 67.8 [CH]; 127.2 [CH]; 127.8 [CH]; 128.3 [CH]; 128.6 [CH]; 129.0 [CH]; 129.4 [CH]; 123.0 [C]; 125.2 [C]; 170.2 [C]; 170.8 [C]. ES-MS^{+}: 411.6 [M+H]; 433.8 [M+Na].
7. Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759.
8. Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, *22*, 2419.

9. Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1995**, *25*, 2275–2284.
10. Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838.
11. Kohn, H.; Sawhney, K. N.; LeGall, P.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1991**, *34*, 2444.
12. Abalain, C.; Langlois, M. *Eur. J. Med. Chem.* **1998**, *33*, 155.
13. Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1997**, *38*, 359–362.