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Tetrahedron Letters 45 (2004) 6109–6111
Tetrahedron Letters

Ugi multicomponent reaction with hydroxylamines: an efficient route to hydroxamic acid derivatives

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Received 13 May 2004; revised 16 June 2004; accepted 16 June 2004
Available online 3 July 2004

Abstract—Ugi condensations with *O*-protected hydroxylamines have been successfully performed in THF using $ZnCl_2$ as activating agent. This synthetic strategy opens up the route to a very convergent assemblage of 'internal' hydroxamic acid derivatives (*N*-acyl-*N*-hydroxypeptides).

Multicomponent reactions have recently become one of the favoured methods to prepare pharmacologically relevant compounds.[1] Among many kinds of multicomponent condensations, the Ugi reaction,[2] discovered more than 40 years ago, is without any doubt the most widely exploited, not only to prepare peptide-like molecules, but also to achieve many different types of other biologically active targets.[3] Shortly after the potential of this multicomponent reaction was disclosed, several *variations on theme* have been proposed, including the use of hydroxylamines as amine component.[4] It has been shown that, depending on the reaction conditions, the use of hydroxylamine leads to substituted hydroxylamines, α-hydroxylamino-*N*-hydroxy amidines, 2-hydroxylaminoamides, 2,2′-imino dicarboxydiamides or hydroxamic acids.[5] Among these products, hydroxamic acids, for their importance as enzyme inhibitors,[6] are certainly the most interesting products formed. However, an examination of the experimental data reveals that such compounds could be obtained only in very low yield by this route, and this explains why, after its disclosure, in spite of its potential, this strategy has been scarcely used in drug discovery.[7]

The recent important biological properties shown by 'terminal' as well as 'internal' hydroxamic acid derivatives as enzyme inhibitors,[6] together with our continuing interest in isocyanide based multicomponent reactions,[8] has prompted us to study more in details the exploitation of hydroxylamine or its derivatives as aminoide component in the Ugi reaction and herein we report some preliminary results of our investigation.

As first approach we decided to perform the reaction under conditions similar to those described by Zinner et al.[4] However, mixing in methanol equimolar amounts of *O*-benzyl hydroxylamine (**1**), isovaleraldehyde (**2**), acetic acid (**3**) and cyclohexyl isocyanide (**4**) (Scheme 1), after more than 7 days at room temperature, no trace of the expected *N*-acyl-*N*-benzyloxy amino acid derivative was present. The result did not change when preformed oxime was used. The reduced reactivity of oximes with respect to amines in Ugi reaction is not an unexpected result. It is known that *O*-alkyl hydroxylamines are less reactive than amines either in condensations with aldehydes[9] and in acyl transfer process,[10] and that the corresponding oximes are less electrophilic than imines in nucleophilic additions.[11] We speculated that, being all these transformations sensitive to acid catalysis, the addition of a Lewis acid to the initial mixture, could have a beneficial effect on the reaction. On the other hand, as demonstrated by Zinner et al.,[4] the use of a mineral acid such as hydrogen chloride leads to substituted hydroxylamines and not to hydroxamic acids.

Lewis acids have been already used in some Passerini[12] or Ugi[13] MCRs with the main purpose of controlling the

Keywords: Ugi multicomponent reaction; Hydroxamic acids; Hydroxylamines; Metalloprotease inhibitors.
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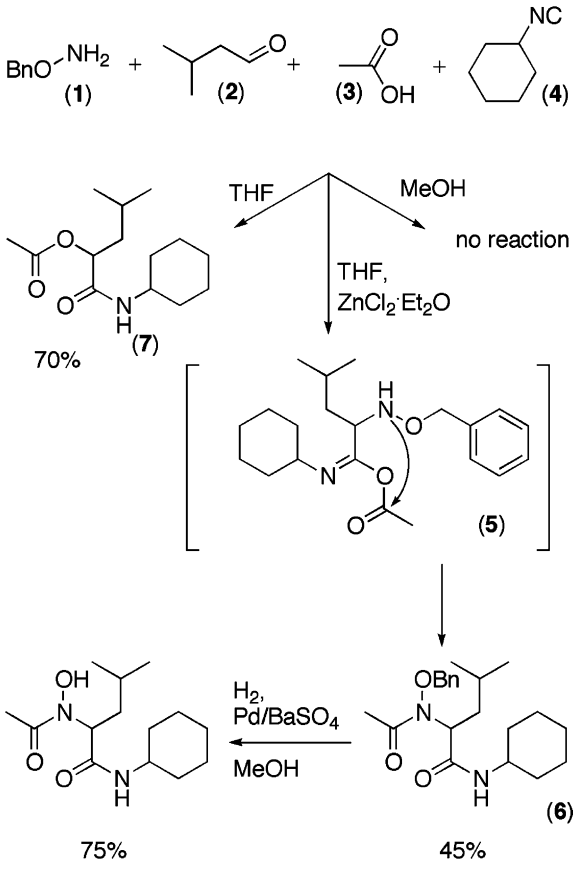
doi:10.1016/j.tetlet.2004.06.068



Scheme 1. Outcomes of the reaction of **2**, **3** and **4** with *O*-benzyl hydroxylamine (**1**) varying the experimental conditions.

stereochemistry of these reactions; based on these reports and on our ongoing experiments on amine-based Ugi reactions,[14] we selected etherated $ZnCl_2$ as Lewis acid of choice[15] and added 1 equiv of this reagent to an equimolar mixture (1 equiv) of the same four components cited before, dissolved in THF (Scheme 1). With our delight, the desired *O*-protected hydroxamic acid (**6**) was formed after 2 days at room temperature, probably via intermediate (**5**) and isolated in 45% yield; the positive effect of the Lewis acid was confirmed by isolation of the Passerini adduct (**7**) as unique product when the same components were left to react in the same solvent for 2 days in absence of $ZnCl_2$. With these results in hands, we moved on to optimise the reaction conditions, finding that the preformed oxime reacted faster, although the final yield was only moderately higher than in the case where the four components and the Lewis acid were mixed together in the reaction vessel. Greater influence on the yield of the final product had the amounts of acid, isocyanide and $ZnCl_2$ used: when all three components were employed in excess (2–3 equiv) with respect to the oxime, the final product could be isolated after 2 days at room temperature in 78% yield. On the other hand, higher temperatures were found to be deleterious.

Having established the optimal conditions for the model reaction, we proved the versatility of this methodology by employing oximes prepared from various aldehydes and by reacting them with different isocyanides and carboxylic acids, as illustrated in Table 1 (entries 1–15). Yields ranged from modest to very good, and peptide-like molecules could be obtained when amino acid derivatives were employed as acid and isocyanide components. When chiral components were used as carboxylic acids, no control of the stereochemistry of the newly generated stereocentre was observed, and the two diastereoisomers were isolated in a 1:1 ratio ca. Despite various attempts, oximes deriving from aromatic aldehydes such as benzaldehyde, 4-nitrobenzaldehyde or 4-methoxybenzaldehyde did not react at all, and the unreacted starting materials could be recovered even after several days. We also investigated the use of *O*-*tert*-butyldimethylsilyl (entry 16) and *O*-unprotected (entry 17) oximes, but in both cases yields of the final products were lower than in the case of the *O*-benzyl protected ones. When the oxime deriving from *O*-silyl protected

Table 1. Ugi reactions with oximes deriving from various hydroxylamines and aldehydes, carboxylic acids and isocyanides[a]

n	Hydroxylamine	Aldehyde	Carboxylic acid	Isocyanide	Yield (%)
1	*O*-Benzyl	Isovaleric	Acetic	Cyclohexyl	78
2	*O*-Benzyl	Isovaleric	Boc-L-valine	Cyclohexyl	41
3	*O*-Benzyl	Isovaleric	Fmoc-L-valine	Cyclohexyl	54
4	*O*-Benzyl	Isovaleric	Cbz-L-phenylalanine	Cyclohexyl	52
5	*O*-Benzyl	Pivalic	Acetic	Ethyl isocyanoacetate	64
6	*O*-Benzyl	Pivalic	Benzoic	Ethyl isocyanoacetate	35
7	*O*-Benzyl	Phenylacetic	Acetic	Ethyl isocyanoacetate	82
8	*O*-Benzyl	Phenylacetic	Benzoic	Ethyl isocyanoacetate	50
9	*O*-Benzyl	Acetic	Butanoic	*t*-Butyl	82
10	*O*-Benzyl	Isobutyric	Butanoic	*t*-Butyl	83
11	*O*-Benzyl	Isobutyric	Boc-glycine	Benzyl	83
12	*O*-Benzyl	Formic	Benzoic	Cyclohexyl	60
13	*O*-Benzyl	Acetic	Boc-glycine	Benzyl	95
14	*O*-Benzyl	Formic	Boc-L-tryptophan	Benzyl	83
15	*O*-Benzyl	Propanal	Boc-L-valine	Ethyl isocyanoacetate	53
16	*O*-TBDMS	Isobutyric	Acetic	Cyclohexyl	27
17	*O*-H	Isobutyric	Acetic	*t*-Butyl	33

[a] Reactions were performed in dry THF under an inert atmosphere at room temperature for 2–3 days with 2–3 equiv of carboxylic acid, isocyanide and $ZnCl_2$ in respect to the oxime. The oximes were preformed by simply mixing the corresponding hydroxylamine and aldehyde at room temperature. Yields are calculated after chromatography. All compounds were fully characterised by NMR and MS analysis.

hydroxylamine and isobutyraldehyde was employed, the final product was isolated with the free hydroxyl group, since the silyl protection did not survive the conditions of the Ugi reaction.

According to a procedure recently reported by Nikam et al.[16] on the deprotection of terminal and internal *O*-benzyl hydroxamic acids, the products of Table 1 obtained from the Ugi condensation with *O*-benzyl hydroxylamine can be debenzylated via hydrogenolysis with $Pd/BaSO_4$, leading to *N*-alkyl hydroxamic acids. We tested this procedure on various compounds, obtaining the debenzylated products with yields ranging from 50% to 90%.

In conclusion, we have reported a very straightforward route to *N*-alkylated hydroxamic acid derivatives via the Ugi four component condensation. This route is highly convergent and easily transferable onto the solid phase (anchoring the hydroxylamine onto the solid support via a Wang-type linker replacing the *O*-benzyl protection)[17] to prepare libraries of potential protease inhibitors. This will be the subject of a subsequent paper.

Acknowledgements

The authors thank MIUR and C4T for financial support.

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