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A new synthesis of β-keto amides by reduction of Passerini adducts

Ana G. Neo,[a] Jose Delgado,[a] Cecilia Polo,[a] Stefano Marcaccini[b] and Carlos F. Marcos[a,*]

[a]*Laboratorio de Química Orgánica y Bioorgánica, LOBO, Departamento de Química Orgánica, Facultad de Veterinaria, Universidad de Extremadura, 10071 Cáceres, Spain*
[b]*Dipartimento di Chimica Organica 'Ugo Schiff', Università di Firenze 50019 Sesto Fiorentino FI, Italy*

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Abstract—The Passerini reaction between glyoxals, isocyanides and acetic acid forms β-keto acyloxyamides, which are readily transformed in β-keto amides by reductive deacetoxylation with zinc. The versatility of this procedure, which allows introducing different groups both in position-3 and the amide nitrogen, makes it ideal for its use in diversity-oriented synthesis, in combination with subsequent complexity generation reactions.

Diversity-oriented synthesis (DOS) has received much attention lately as a tool for the exploration of the chemical space of molecular structures.[1] The aim of DOS is to obtain collections of small molecules as complex and diverse as possible. The screening of such molecular libraries, searching for perturbing effects on disease-related biological pathways, may eventually lead to the identification of therapeutic protein targets, which can be modulated by small organic molecules. The development of effective strategies in DOS is therefore very important in finding new pharmacological targets.[2] Multicomponent reactions (MCRs) are privileged in the generation of molecular complexity, and have proven to be very useful in DOS.[3,4] A remarkable feature of MCRs is their capability to generate multifunctional compounds from simple monofunctional starting materials. Multifunctional reagents, in turn, serve as advantageous starting materials for the construction of libraries of more complex molecules.

As part of our research in the use of MCRs for the synthesis of heterocyles,[5] we were able to prepare several furan,[6] indole[6a] and oxazole[7] derivatives by the Passerini condensation[8] of arylglyoxals, carboxylic acids and isonitriles, followed by suitable post-condensation transformations.[9] However, this method is limited to the use of carboxylic acids containing particular structures or functional groups. On the other hand, reductive removal of the acyloxy group in the 2-acyloxy-3-keto amides (**4**) coming from the Passerini condensation of arylglyoxals would give β-keto amides (**5**), containing an active methylene group suitable for further functionalization. In fact, β-keto amides (**5**) have proven to be versatile building blocks in the synthesis of different heterocycles, as pyrroles,[10] indoles,[11] tetrahydroquinolines,[12] dihydropyrimidones,[13] dihydrofuranodiones and succinimides.[14] So, this strategy would, in theory, allow preparing a wide range of heterocyclic structures.

Several methods have been previously reported for the synthesis of β-keto amides (**5**). The most general ones are based on nucleophilic amidation of electrophiles, as β-keto acids,[15] β-keto esters,[16] β-keto thioesters,[17] ketene dimers,[18] dioxinones[19] or acylated Meldrum's acids.[20] Other approaches include condensation of ketone enolates with isocyanates[21] or activated carbamates,[22] condensation of amide enolates with esters[23] or acyl chlorides,[24] isoxazolium salts fragmentation,[25] and enzymatic hydrolysis of β-keto nitriles.[26] Nevertheless, many of these methods have limitations, as they involve very specific or low yielding reactions, use harsh reaction conditions, or require difficult syntheses of the starting materials.

Rosenfeld has reported the deacetoxylation of esteroid ketol acetates using zinc in refluxing glacial acetic acid.[27] A modification of this method, using ultrasounds, has been applied to the cleavage of sesquiterpene γ-enonelactones.[28] In our case, we envisaged that the reductive

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* Corresponding author. Tel.: +34 927 257158; fax: +34 927 257110; e-mail: cfernan@unex.es

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deacyloxylation of 2-acyloxy-3-keto amides (**4**) with zinc would be facilitated by the complexation of a zinc atom by the two carbonyl groups of the substrate.

With all these considerations in mind, we propose a straightforward method for the preparation of β-keto amides (**5**) by a Passerini three-component condensation, followed by zinc promoted removal of the acid component.

The combination of glyoxals (**1**) with isocyanides (**2**) and acetic acid (**3**) gave the expected Passerini three-component adducts (**4**; Table 1). The reaction is conveniently performed by mixing the three components in diethyl ether and stirring at room temperature for 3 days. Typically, the yields are moderate to good and, in most of the cases, the adduct precipitates in the reaction medium, and is isolated with high degree of purity by simple filtration. Though, in a few cases, hexane is added to the reaction medium in order to induce precipitation of the product.

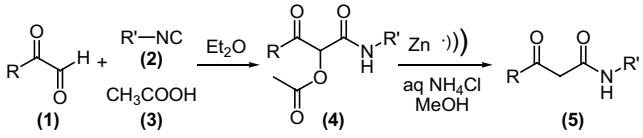
Subsequent reduction of the Passerini adducts takes place almost instantaneously, in extraordinarily mild conditions, using activated zinc in a mixture of saturated aqueous ammonium chloride and methanol. Addition of water promotes the precipitation of the products, which can then be isolated by filtration and, according to our experience, directly used in further reactions. However, purification by column chromatography was systematically carried out, in order to get reproducible yields and analytically pure samples. Cleavage of the acetoxy group was evidenced by the loss of the carboxylic C=O stretching peak at around 1750 cm^{-1} in the IR spectra. In this way, β-keto amides (**5**) are obtained, in good or excellent yields, and essentially pure, as showed by TLC analysis, and confirmed in one case by HPLC (UV detection at 214 and 300 nm). Though, in most of the cases tautomerization takes place in solution, so NMR spectra show peaks corresponding to the minor enol form, in addition to the main signals corresponding to the major keto form.[22,24,26] Their structures were confirmed by the usual analytical and spectroscopic methods.

In this two-step process, only the fragments coming from the aldehyde and isocyanide components are present in the final structure. The acid component is useful in the construction of the desired molecular skeleton and the acetoxy on the Passerini adduct is actually masking an active methylene group, which is just revealed after the reduction with zinc. The transformation of the Passerini adducts into β-keto amides could be used as a branching strategy in DOS.[29]

It is noteworthy that, the cleavage of the acetyl group takes place in aqueous medium, in very mild conditions, as anticipated. We propose a mechanism in which an initial complexation of a zinc atom with the ketone and amide carbonyl groups in the Passerini adduct takes place. The formation of this complex forces a flat conformation of the bidentate ligand, facilitating the donation of a pair of electrons from zinc to the ketone oxygen. This results in the formation of the corresponding conjugated zinc enolate and the concomitant release of the acetate leaving group. Neutralization and tautomerization gives the final β-keto amides (Scheme 1).

As many different arylglyoxals and isocyanides are easily available, a wide variety of substituents can be introduced both in position-3 and in the amide nitrogen. From this point of view, the present route appears to be more versatile than many of the earlier approaches to β-keto amides. On the other hand, it is experimentally very simple, and both the Passerini adducts and the final β-keto amides can be easily isolated with a reasonable grade of purity by filtration. Hence, although our method

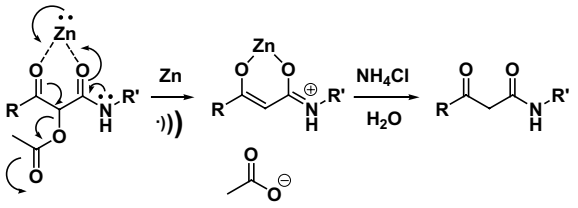
Table 1. Synthesis of β-keto amides



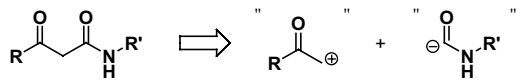
	4, 5	R	R′	% 4[a]	% 5[b]
1	**a**	C_6H_5	C_6H_{11}	74	82
2	**b**	4-Me–C_6H_4	C_6H_{11}	73	74
3	**c**	4-Cl–C_6H_4	C_6H_{11}	76	83
4	**d**	4-Br–C_6H_4	C_6H_{11}	77	71
6	**e**	C_6H_5	C_5H_{11}	73	68
7	**f**	4-Br–C_6H_4	C_5H_{11}	68	66
5	**g**	C_6H_5	$PhCH_2$	60	70
8	**h**	4-Me–C_6H_4	$PhCH_2$	74	69
9	**i**	4-Cl–C_6H_4	$PhCH_2$	63	84
10	**j**	4-Br–C_6H_4	$PhCH_2$	82	73
11	**k**	C_6H_5	^{t}Bu	89	80
12	**l**	4-Me–C_6H_4	^{t}Bu	81	76
13	**m**	4-Br–C_6H_4	^{t}Bu	66	67
14	**n**	C_6H_5	2,6-Me_2Ph	81	87
15	**o**	4-Me–C_6H_4	2,6-Me_2Ph	69	94
16	**p**	4-(MeO)–C_6H_4	2,6-Me_2Ph	78	85
17	**q**	4-Cl–C_6H_4	2,6-Me_2Ph	67	95
18	**r**	4-Br–C_6H_4	2,6-Me_2Ph	75	95
19	**s**	C_6H_4	4-(MeO)–Ph	75	74

[a] 5 mmol of each acetic acid and the corresponding arylglyoxal and isocyanide were stirred 72 h in Et_2O at room temperature. Filtration and washing with *i*-PrOH and *i*-Pr_2O yielded the product pure enough to be used in the following reaction.

[b] 8 mmol of Zn dust in 8 mL of saturated aqueous NH_4Cl is activated by irradiation 5 min in a sonication bath; 2 mmol of the starting Passerini adduct dissolved in 32 mL of methanol was then added, and the mixture was stirred 30 min at room temperature. Zn was filtered off, 100 mL of water was added, and the resulting white precipitate was filtered, dried under vacuum and purified by flash column chromatography. The yields have not been optimized.



Scheme 1. Proposed mechanism for the zinc deacetoxylation of β-keto amides.



Scheme 2. Formal double-Umpolung disconnection for the synthesis of β-keto amides.

involves two separate reaction steps, in some cases it may be advantageous relative to apparently more straightforward procedures, as the one-step thermal reaction of β-keto esters with primary amines; for example, in combinatorial chemistry applications. Several examples combining different arylglyoxals and aliphatic an aromatic isocyanides are reported in Table 1 and the yields for both the Passerini condensation and zinc reduction are given. All the isocyanides employed were obtained from commercial sources, while glyoxals were made by oxidation of the corresponding acetophenones with HBr in DMSO.[30]

In summary, a simple and versatile two-step synthesis of β-keto amides has been developed. This method formally involves the formation of a new bond between a β-keto-carbocation and a carbamoyl anion. This means that the β-keto amide moiety is built through an unusual double Umpolung process (Scheme 2). To our knowledge, such disconnection has never been employed before in the preparation of β-keto amides. The use of recyclable polymer supported carboxylic acids in the Passerini condensation, which would spare the sacrificial use of acetic acid, is currently under research in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.041.

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