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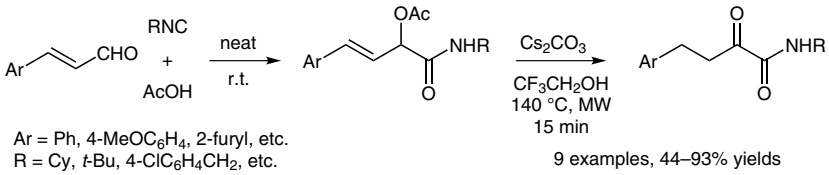
A Nonoxidative Passerini Pathway to α-Ketoamides

Abdelbari Ben Abdessalem[a,b]
Raoudha Abderrahim*[b]
Laurent El Kaïm*[a]

[a] Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA ParisTech- UMR 7652, Universtité Paris-Saclay, 828 Bd des Maréchaux, 91128 Palaiseau, France
laurent.elkaim@ensta-paristech.fr
[b] Département de Chimie, Faculté des Sciences de Bizerte, Université de Carthage, Tunisia, abderrahim.raoudha@gmail.com



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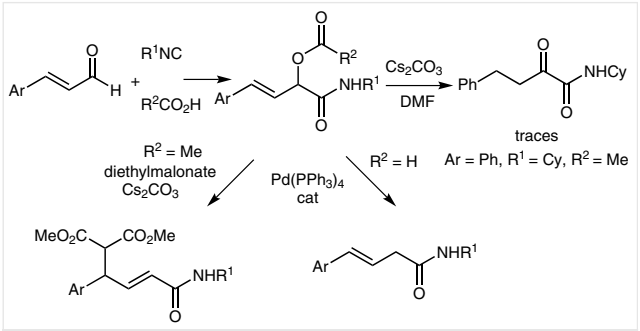
Abstract The Passerini adducts of cinnamaldehyde derivatives may be efficiently converted into α-ketoamides when heated with a base under microwave conditions.

Key words Passerini, isocyanide, α-ketoamide

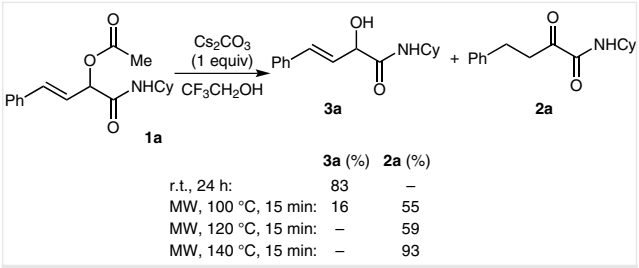
α-Ketoamides have been the object of considerable attention both as synthetic intermediates and as targets in medicinal chemistry. Indeed, the integration of an α-ketoamide unit into amino acid derivatives has led to the disclosure of important families of reversible proteases inhibitors such as the Hepatitis C virus serine protease,[1] calpain,[2] or the NS2B-NS3 Dengue virus protease.[3] The α-ketoamide function is also present as a key pharmacophore in FK-506 or Rapamycin, natural products with interesting immunosuppressive activity.[4] Among the various synthetic methods available for their preparation,[5] the use of isocyanide-based coupling reactions has been particularly useful as the ketoamides may be obtained from readily available acyl chlorides or aldehydes. Isocyanide addition to acyl chlorides (Nef isocyanide reaction) followed by hydrolysis affords one of the most straightforward preparation of α-ketoamides[6] whereas the use of aldehydes in Passerini reactions[7] requires a final oxidation of an intermediate α-hydroxyamide.[8] α-Ketoamides have also been obtained via different Ugi/oxidation sequences[9] or through using directly hydroxylamine as the amino partner in the Ugi coupling.[10] Herein, we wish to present a new conversion of cinnamaldehydes into α-ketoamides via a Passerini/saponification sequence.

Following our interest in palladium-triggered transformation of multicomponent adducts derived from isocyanide, we recently became interested in the use of cinnamaldehyde in Passerini reactions[11] and showed that the choice of formic acid as acidic partner in the Passerini step afforded suitable adducts for efficient Tsuji–Trost reduction (Scheme 1,A).[12] Different nucleophilic carbon species were then successfully added to related Passerini adducts (Scheme 1,B).[13] During the evaluation of the scope of these additions, we obtained under forcing conditions with some poorer nucleophiles a decomposition of the Passerini adducts with the formation of traces of α-ketoamides. The same was observed under heating with a base in the absence of palladium catalyst (ketoamide **2a**, Scheme 1,C). As this reaction might afford a simple and convenient access to ketoamides, we decided to study further this transformation.



Scheme 1 Tsuji–Trost reactions of Passerini cinnamaldehyde

The formation of **2a** may be explained by a two-step process involving a saponification of the ester and an isomerization of the double bond. To improve the fragmentation step the use of different combinations of protic solvent and bases were explored. While the use of ethanol (with NaOEt, K_2CO_3 or Cs_2CO_3) was rather deceiving giving either mixtures at higher temperature or unreacted starting material, the choice of trifluroethanol as solvent was more gratifying. When **1a** was treated at room temperature with one equivalent of Cs_2CO_3 for 24 hours only the alcohol **3a** was obtained in 83% isolated yield (Scheme 2). When the reaction was performed at 100 °C under microwave conditions (15 min) we were pleased to observe the formation of the expected **2a** isolated in 55% yield along with a small amount

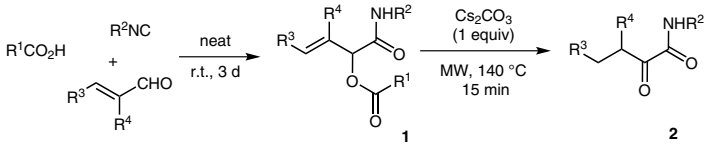


Scheme 2 α-Ketoamide formation from Passerini adduct **1a**

of **3a**. Raising the temperature to 140 °C led to a complete conversion to **2a** obtained in 93% yield after a simple filtration on silica gel.

These conditions were selected to perform the conversion of various Passerini adducts **1** into ketoamides **2** (Table 1).[14] Several carboxylic acids were engaged in the Passerini step to evaluate the influence of the ester moiety on the yields of the ketoamide formation. Acetic acid appears to be the best carboxylic acid partner for this sequence giving higher yields those obtained with pivalic acid (Table 1, entry 1 versus entry 2) or benzoic acid (Table 1, entry 3 versus entry 4). The ketoamide synthesis shows a strong dependence on the nature of the *N*-amide substituent. *N*-Cyclohexylamide (Table 1, entries 1, 2, 7, 8, 10 and 11) gave good yields of ketoamides whereas an *N*-*tert*-butyl group led to slightly lower yields (Table 1, entries 5 and 9) and a *N*-4-chlorobenzyl group gave much lower yields (Table 1, entries 3 and 4).

Table 1 Conversion of Various Passerini Adducts **1** into Ketoamides **2**



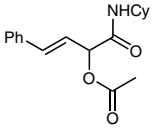
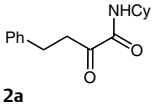
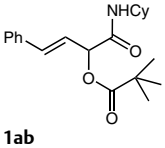
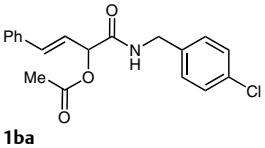
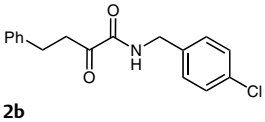
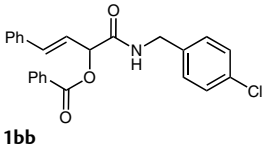
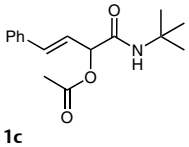
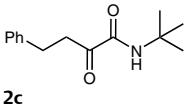
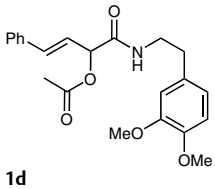
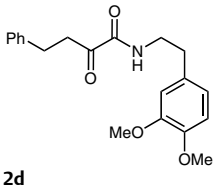
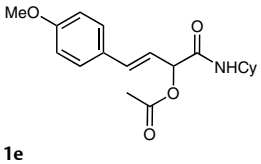
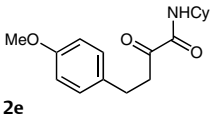
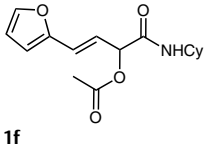
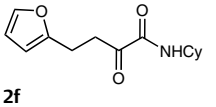
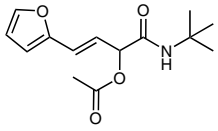
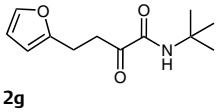
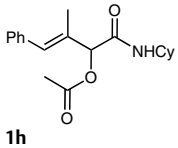
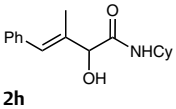
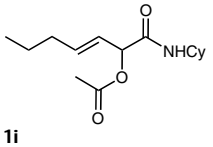
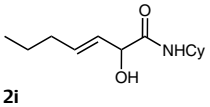
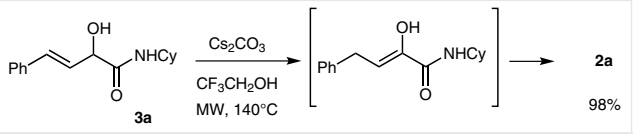
Entry	1	Yield (%)	2	Yield (%)
1	 **1aa**	84	 **2a**	93
2	 **1ab**	63	**2a**	83
3	 **1ba**	77	 **2b**	53
4	 **1bb**	84	**2b**	28
5	 **1c**	70	 **2c**	82

Table 1 (continued)

Entry	1	Yield (%)	2	Yield (%)
6	 **1d**	79	 **2d**	44
7	 **1e**	60	 **2e**	74
8	 **1f**	79	 **2f**	75
9	 **1g**	66	 **2g**	70
10	 **1h**	62	 **2h**	92
11	 **1i**	60	 **2i**	68

The two-step sequence may be performed on various cinnamaldehyde analogues as shown by the successful formation of ketoamides from the 4-methoxyaryl derivative **1e** (Table 1, entry 7) or the substituted furans **1f** and **1g** (Table 1, entries 8 and 9). Indications on the mechanism of the reaction may be given from the attempted formation of α-ketoamide from Passerini adduct **1i**. Under our standard conditions, allylic alcohol **3i** was the only product we could recover (Table 1, entry 11). This may be explained by the higher acidity of aryl-substituted allyllic esters **1a**–**1g** compared to **1i**. With the former Passerini adducts, Cs_2CO_3 is basic enough to deprotonate the α-position of the amide leading to a migration of the double bond in the protic solvent. The ability of related Ugi adducts of cinnamaldehyde to be depronated at this position has already been reported in various preparations of heterocycles.[15] The inability of **1h** to be transformed into an α-ketoamide (Table 1, entry 10) may probably be explained following the same line as even if an aryl substituent should increase the acidity, the steric effect of the methyl group on the double bond probably limits the formation of a planar conjugated anion. Whenever the acidity of alcohols **3** is not lowered by such factors, cesium carbonate is expected to be basic enough for the isomerization of **3** into **2**. This was further confirmed by the high-yielding transformation of **3a** into **2a** under the same conditions (Scheme 3).



Scheme 3 Isomerization of **3a** into **2a**

To conclude, we have proposed an alternative formation of α-ketoamides using isocyanide-based multicomponent reactions. Though the process is limited to the formation of ketoamides substituted at the 4 position by aryl or heteroaryl groups, the addition of transition metals prone to trigger allylic alcohol isomerization may be envisioned for aliphatic derivatives.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560632.

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(14) Typical Procedure for **2a**: The Passerini adduct **1a** (102 mg, 0.338 mmol) and Cs_2CO_3 (1.0 equiv, 110 mg) were suspended in trifluoroethanol (TFE; 3.0 mL) in a 10-mL reaction glass vial containing a magnetic stir bar. The vial was flashed with argon, sealed and irradiated with stirring (CEM Discover Microwave. Settings: 140 °C, 150 W) during 15 min. Upon completion of the reaction time, the vial was cooled to r.t. The reaction mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Purification by flash column chromatography on silica gel (CH_2Cl_2–petroleum ether, 20:80) gave **2a** as a white solid (mp 86.0–86.5 °C) isolated in 93% yield (81 mg); R_f 0.6 (CH_2Cl_2–petroleum ether, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.30 (m, 2 H, H-Ar), 7.17–7.22 (m, 3 H, H-Ar), 6.82 (d, *J* = 6.3 Hz, 1 H, NH), 3.67–3.77 (m, 1 H), 3.28 (t, *J* = 7.5 Hz, 2 H), 2.93 (t, *J* = 7.5 Hz, 2 H), 1.87–1.91 (m, 2 H, H-Cy), 1.60–1.76 (m, 3 H, H-Cy), 1.32–1.42 (m, 2 H, H-Cy), 1.13–1.25 (m, 3 H, H-Cy). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.8, 159.0, 140.5, 128.6, 128.5, 126.3, 48.4, 38.4, 32.7, 29.2, 25.4, 24.8. HRMS: *m*/*z* calcd for $C_{16}H_{21}NO_2$: 259.1572; found: 259.1564. IR ($CHCl_3$): 3398, 2938, 2858, 1720, 1682, 1522, 1498, 1453, 1373, 1116, 892 cm^{-1}.
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