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Three in the spotlight: photoinduced stereoselective synthesis of (Z)-acyloxyacrylamides through a multicomponent approach

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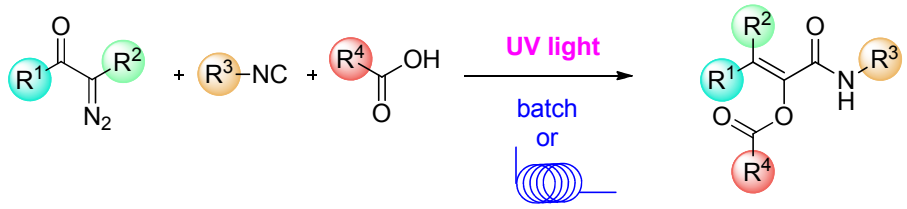


Abstract

We report a straightforward approach to 2-acyloxyacrylamides, useful synthons in organic synthesis. This involves a photoactivated multicomponent reaction, performed both in batch and under continuous flow conditions, and affords the desired compounds in a stereoselective fashion from readily available starting materials in one step, without the aid of metal catalysis. This paper illustrates the preliminary work, the extensive experiments carried out to understand the limitations of the approach and the optimization of the conditions for the synthesis of these particular captodative olefins.

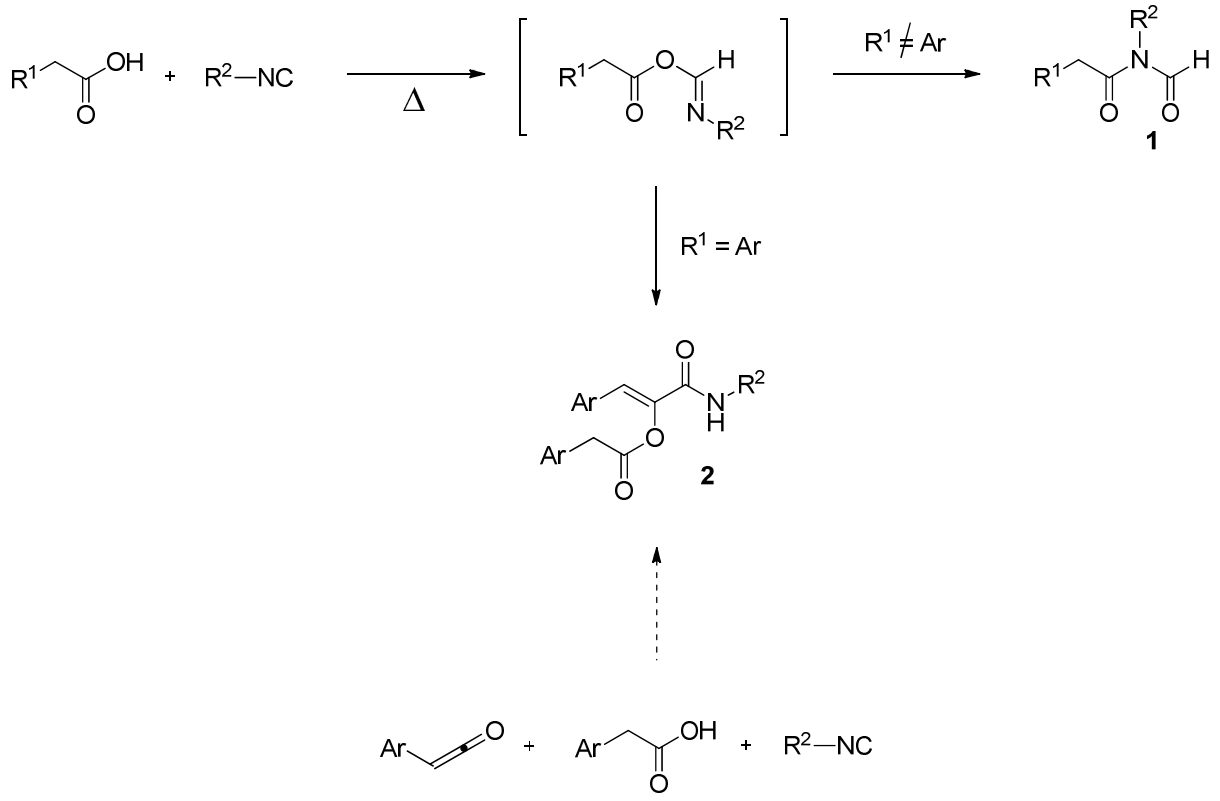
Introduction

Among acrylic derivatives, 2-acyloxyacrylates have captured special interest owing to the opposite electronic demand and to the synthetic potential displayed by the geminally substituted double bond.[1] These captodative olefins have proved to be versatile synthons, efficiently employed in Diels-Alder condensations, 1,3-dipolacycloadditions and Friedel-Craft reactions, to name a few.[2]

We have recently discovered that the corresponding amides can rearrange under basic conditions to afford novel 5-membered ring heterocycles endowed with biological activity.[3] With the aim of finding a general route to 2-acyloxyacrylamides, we have discovered a multicomponent reaction between ketenes, isocyanides and carboxylic acids. A preliminary report has been recently published.[4] We wish now to report full details of this novel three component condensation.

Results and Discussion

Use of acyl chlorides for the generation of ketenes. In 2008 Danishefsky reported the sequential concerted rearrangement occurring in the coupling between isocyanides and carboxylic acids, leading to N-formylamides **1**.[5] One year later we have observed that the reaction pathway is different when arylacetic acids are employed; in this case, in fact, captodative olefins **2** incorporating two molecules of acid and one of isocyanide are formed (Scheme 1).[6] Reasoning on the possible mechanism taking place in this instance, we postulated that the same outcome could be achieved when an arylketene reacts with one molecule of arylacetic acid and one of isocyanide through a formal Passerini reaction.[7]

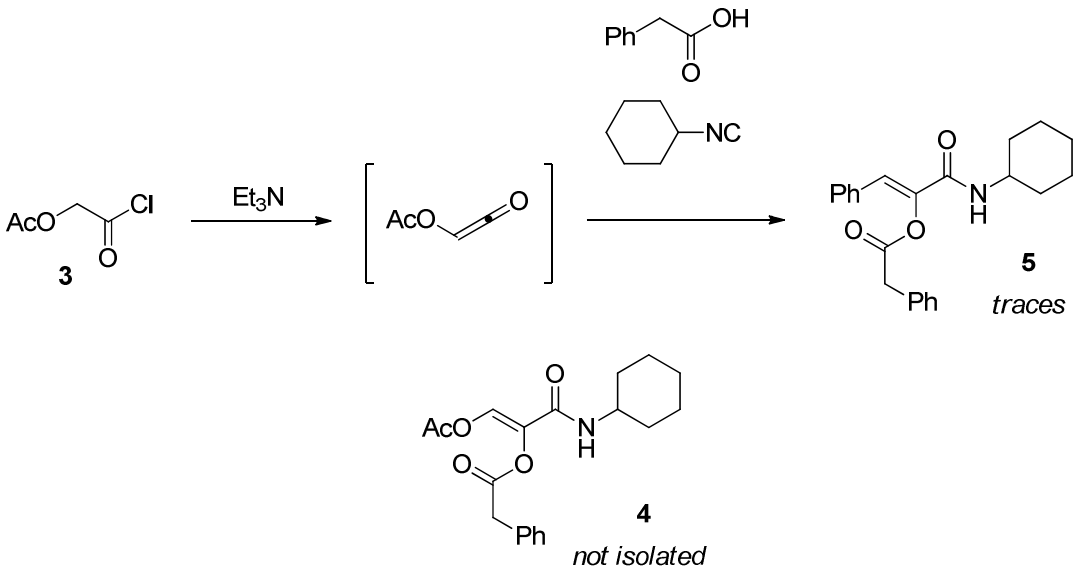


Scheme 1. The different fate of carboxylic acids and isocyanides. A possible alternative route to compounds **2**.

In the literature there are some precedents of the reactivity of ketenes and isocyanides. For example, in 1961 Ugi reported the reaction between isocyanides and two equivalents of diphenylketene, affording 1,3-dioxolan-4-imine derivatives.[8] Twenty years later Capuano showed the versatility of the reaction between isocyanides and ketenes obtaining, according to one of the first diversity-oriented approach, a plethora of different heterocycles.[9] More recently, Pirali reported that isocyanoacetamides react with in situ generated ketenes, affording aminooxazoles.[10]

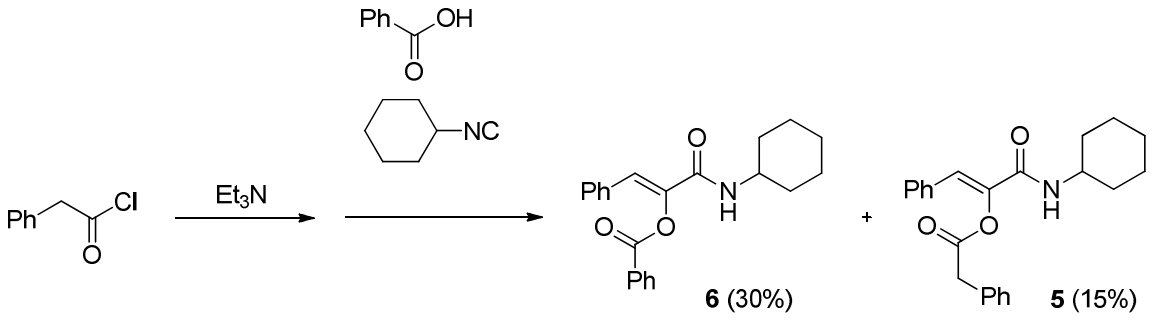
Nevertheless, to the best of our knowledge the use of ketenes in multicomponent reactions has never been explored so far, if we exclude the condensation with thiazolium salts and dimethyl acetylenedicarboxylate reported by Ma.[11]

When we started this project we were aware of the difficulties we could have encountered, related to the instability and high reactivity of ketenes. Indeed, our first attempts to generate acetoxyketene from acetoxyacetyl chloride **3** in the presence of triethylamine at room temperature and to react it with cyclohexyl isocyanide and phenylacetic acid failed to afford the desired product **4**. Interestingly, traces amounts of compound **5** were isolated (Scheme 2).



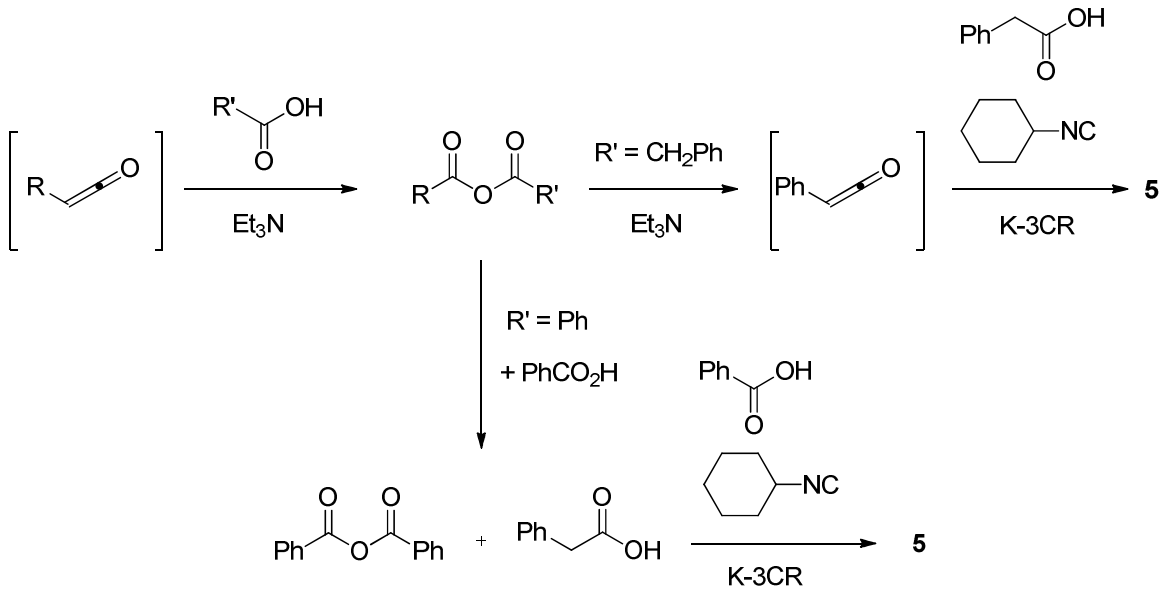
Scheme 2.First attempts to the ketene three component reaction (K-3CR).

When the same reaction was attempted with phenylacetyl chloride and benzoic acid the multicomponent adduct **6** was isolated in 30% yield, but compound **5** was also formed (15%) (Scheme 3).



Scheme 3. Formation of *hetero*-adduct **6** and *homo*-adduct **5** from the K-3CR.

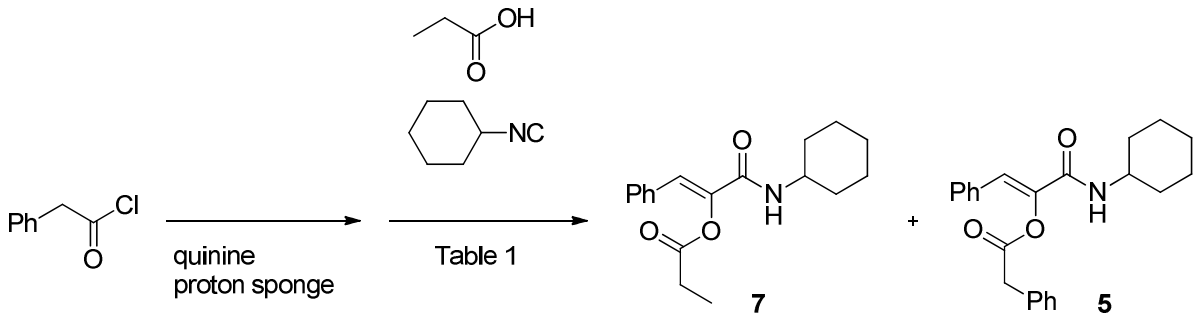
These preliminary results already showed the main limitation of this approach. In order to explain formation of *homo*-adduct **5** from both attempts, we postulated that, under the basic medium generated by triethylamine, the ketene, once formed from the acyl chloride, can alternatively react with the isocyanide or the carboxylic acid. In the latter case a mixed anhydride is produced and this in turn can re-generate a molecule of ketene (the same one or the one deriving from the acid) or can react with an additional molecule of carboxylic acid to form the symmetrical anhydride, thus liberating the initial acyl chloride as its corresponding carboxylic acid. Re-generation of a ketene explains formation of **5** from the first reaction: phenylketene, stabilized by the conjugation with the aromatic ring, could have a longer life-time compared to acyloxyketene, longer enough to react with cyclohexylisocyanide and additional phenylacetic acid to give the K-3CR. On the other hand, liberation of phenylacetic acid from the mixed benzylphenylanhydride can explain formation of **5** from the second reaction, where it can compete with benzoic acid to form the multicomponent adduct (formation of phenylacetic acid as a consequence of the reaction of the chloride with traces amounts of water was ruled out by employing molecular sieves) (Scheme 4).



Scheme 4. The side formation of a mixed anhydride could explain formation of adduct **5** from the previously described attempts.

By searching alternative methods to generate ketenes, we came across the works by Lectka, employing the "shuttle deprotonation" system.[12] By using a catalytic amount of a "kinetic base" (quinine) and a stoichiometric amount of an insoluble "thermodynamic base" (proton sponge), under anhydrous conditions, we could dramatically improve the outcome of the reaction. Generation of the ketene from phenylacetyl chloride was performed in toluene at -78 °C, and a DCM solution of cyclohexyl isocyanide and benzoic acid was added after 10 mins. at the same temperature. The temperature was left rising overnight and, upon work-up and chromatographic purification, compound **6** was isolated in 71% yield, although contaminated by a small amount (6%) of "homo" adduct **5**. By doubling the amount of benzoic acid, the yield could be slightly improved (82%) and the amount of **5** slightly reduced (4%).

With these promising results in hand, we extended the improved methodology to other carboxylic acids. However, results were disappointing and high amounts of "homo" adduct were isolated together with the desired products. For example, when propionic acid was employed, crude material contained the desired product **7** and compound **5** in a 2:1 ratio (Scheme 5). This reaction was taken as a model to study in details the influence of the reaction conditions on the formation of **5**. The results are summarized in Table 1.



Scheme 5. K-3CR with phenylacetyl chloride, propionic acid and cyclohexyl isocyanide.

Table 1. Study of the influence of reaction parameters on the outcome of the K-3CR with phenylacetyl chloride, propionic acid and cyclohexyl isocyanide.

Entry	Reagents ratio[a]	Conc.	Conditions	7/5 ratio (%)
a	1.0:0.9:2.0	0.2M	addition of isocyanide and acid in DCM at -78 °C, then temperature gradually raised to r.t. in 24 hrs	1.0:0.50 (57%)
b	1.0:0.9:2.0	0.1M	conditions **a**	1.0:0.45 (62%)
c	1.0:0.9:2.0	0.2M	conditions **a**, but reaction immediately at r.t. after addition	1.0:0.40 (46%)
d	1.0:0.9:2.0	0.2M	conditions **a**, but acid is added after 2hrs at -70 °C, then temperature gradually raised	1.0:0.10 (10%)
e	1.0:0.9:-	0.2M	conditions **a**, but propionic anhydride (1.0 eq) is used instead of propionic acid	-
f	1.0:0.9:0.9	0.1M	conditions **a**	1.0:1.4 (64%)
g	1.0:0.9:5.0	0.1M	conditions **a**	1.0:0.20 (29%)
h	1.0:0.9:2.0	0.2M	conditions **a,** but isocyanide and acid added neat	1.0:0.42 (73%)
i	1.0:0.9:2.0	0.1M	isocyanide and acid from the beginning, then acyl chloride dropwise at -78 °C	1.0:0.53 (75%)
j	1.0:0.9:2.0	0.1M	conditions **a**, using Et_3N as a base (no shuttle system)	-
k	1.0:0.9:2.0	0.1M	conditions **h**, but acid added 20 mins. after the isocyanide (at -70 °C)	1.0:0.49 (76%)

[a]acyl chloride/isocyanide/carboxylic acid

In light of these results it was clear that the **7**/**5** ratio could be improved only at the expense of the overall yield, and that generation of the mixed anhydride, responsible for the formation of **5**, was a competing process difficult to be prevented and highly dependent on the nature of the carboxylic acid. For example, acetyl chlorides lacking an α-aryl group failed to react under the above mentioned conditions.

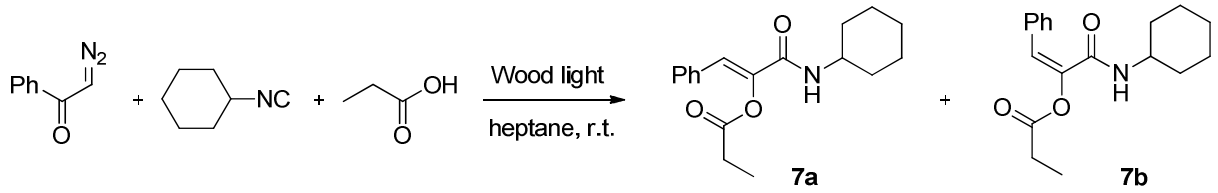
This novel strategy, leading to the desired captodative olefins, although straightforwardly, was not pursued further due to this limitation, and alternative methods for the generation of ketenes were taken into consideration.

Use of diazoketones for the generation of ketenes

Ketenes can be efficiently generated from diazoketones through the Wolff rearrangement. This process can be performed in the presence of metal salts, induced by irradiation or by heating. Many methods employing silver catalysts have been reported in the literature, although many of them use an added base, that in our case would give the same side reactions of the previous methodology. We therefore decided to employ the method developed by Sewald, with silver benzoate in dioxane.[13] In a control experiment phenyldiazoketone was sonicated in the presence of a catalytic amount of

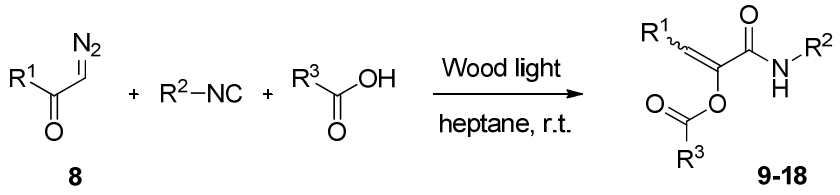
silver benzoate and its disappearance was monitored by TLC. In a second experiment the reaction was performed in the presence of methanol, and methyl phenylacetate was isolated as the sole product. However, when the Wolff rearrangement was attempted in the presence of cyclohexyl isocyanide and propionic acid, no reaction took place and the diazoketone was recovered unreacted. The ability of isocyanides to complex metal ions is known, and probably also in this case silver ions were sequestrated by the reagent.

We therefore moved to investigate the photochemical reaction of diazoketones, having access to a Ryonet merry-go-around apparatus equipped with UV lamps at various wavelengths. Upon irradiation of a heptane solution of equimolar quantitites of phenyldiazoketone, cyclohexylisocyanide and propionic acid with Wood light (maximum wavelength at 365 nm, see emission spectra in supporting information) for one hour, we were pleased to find that the desired olefin **7** was formed and precipitated from the reaction medium. The reaction was not complete, as ca. 50% of diazoketone remained unreacted, but at this stage no trace of compound **5** could be detected on the crude, demonstrating that under neutral/slightly acidic conditions phenylacetic acid was not generated as side product. In a second experiment the reaction mixture was irradiated for four hours, time required by the diazoketone to be completely consumed. The product **7** was isolated, after chromatographic purification, in 65% yield, however the ^{1}H-NMR showed the presence of two substances in a 1.0:0.2 ratio. The relatively similar NMR pattern of the two compounds led us to hypothesize that we had obtained a mixture of the two stereomeric olefins **7a** and **7b** (Scheme 6). It is worth noting that the previously developed reactions leading to captodative olefins always afforded (Z)-acrylamides as the sole geometric isomers, as demonstrated by NOE experiments and theoretical calculations.[6]



Scheme 6. The outcome of the photoinduced K-3CR

In light of this unexpected result, we performed different experiments using different diazoketones **8** in combination with various isocyanides and carboxylic acids (Scheme 7). As illustrated in Table 2, in all cases the desired captodative olefin could be isolated in moderate to good yield, although as a, often unseparable, mixture of isomers. Only for compound **9** (entry **a**) the reaction was completely stereoselective. Nevertheless, contamination by the *"homo"* adducts was never observed, and no excess of one of the reagents was required to drive the reaction to completion, as often occurs in multicomponent condensations. Moreover, also diazoketones lacking conjugation with an aromatic ring (entries **f-h**) succeeded in giving the desired products, thus overcoming a limitation of the previously developed methodologies and allowing for the preparation of captodative olefins with increased structural diversity.



Scheme 7. General scheme of the photoactivated K-3CR

Table 2. Investigation of the scope of the photoactivated K-3CR

entry	R^1	R^2	R^3	compd.	yield (*Z*)	*Z/E*
a	phenyl	cyclohexyl	phenyl	**9**	72%	1:0
b	phenyl	cyclohexyl	3'-MeO-benzyl	**10**	65%	1:0.4
c	2-thiophenyl	cyclohexyl	phenyl	**11**	37%	1:0.8
d	phenyl	butyl	3'-MeO-benzyl	**12**	56%	1:0.5
e	phenyl	*tert*-butyl	3'-MeO-benzyl	**13**	56%	1:0.4

f	4-Cl-phenyl	2-$(MeO)_2$-ethyl	propyl	**14**	68%	1:0.2
g	4-Cl-phenyl	cyclohexyl	propyl	**15**	75%	1:0.1
h	benzyl	cyclohexyl	phenyl	**16**	55%	1:0.1
i	benzyl	cyclohexyl	3'-MeO-benzyl	**17**	62%	1:0.1
j	3-Cl-propyl	cyclohexyl	penta-1,3-dienyl	**18**	43%	1:0.1

Our efforts were therefore directed towards the obtainment of a stereoisomerically pure product. In the case of compound **12**, we succeeded in separate the two isomers by chromatography, and we could therefore confirm their structure as (*Z*)-**12** (the major isomer) and (*E*)-**12** (the minor one). In particular, compound (*Z*)-**12** showed a NOE interaction between the olefinic and amidic hydrogens, while no interaction was observed in the case of (*E*)-**12**, confirming previous results and our initial hypothesis. In light of this, it could be postulated that *Z/E* isomers could derive from a different K-3CR mechanism occurring under UV light irradiation or, alternatively, the (*E*)-isomer could be the result of the isomerization of the (*Z*)-multicomponent adduct, generated according to the standard mechanism. However, the following evidences prompted us to consider the second option more plausible: a) irradiation of pure (*Z*)-isomer under the same reaction conditions generated a *Z/E* mixture (photoisomerization of alkenes is indeed a well-known process); b) when the multicomponent reaction was performed with a delayed timing (1 hour of irradiation and 1 hour in the dark repeated four times) the yield was comparable but the *Z/E* ratio was improved (prolonged times facilitated precipitation of the product off the solvent, thus subtracting it from its isomerization in solution); c) in the case of compound **9** only the (*Z*)-isomer was isolated from the multicomponent reaction, and in fact the (*Z*) to (*E*) photoisomerization was very slow under the same conditions (no appreciable isomerization after irradiation with Wood's light for 3 hours); d) no *Z/E* isomerization was ever observed without irradiation (thus ruling out mechanisms different from those previously illustrated), even upon microwave heating.

We took into consideration factors that could influence the alkene photoisomerization, such as solvent, wavelength and presence of additives such as photosensitizers and photoquenchers. We took as a model the reaction between phenyldiazoketone, butylisocyanide and 3'-

methoxyphenylacetic acid (entry **d**) and carried out a detailed study, where the *Z/E* isomer ratios were calculated by ^{1}H-NMR on the crude and the yields were determined on the isomeric mixture after chromatographic purification. The results are summarized in Table 3.

Table 3. Investigation of the influence of reaction parameters on the outcome of the K-3CR leading to **12**

entry	solvent	UV[a]	Additive (eq)	Time (h)	*Z/E* ratio	yield (*Z* + *E*)
a	heptane	C	-	3h	1:0.14	75%
b	chloroform	C	-	3h	1:0.40	73%
c	diisopropylether	C	-	3h	1:0.50	62%
d	toluene	C	-	3h	1:0.10	73%
e	acetone	C	-	3h	1:0.06	68%
f	heptane	B	-	1.5h	1:0.50	46%
g	heptane	A	-	2h	1:0.80	38%
h	heptane	C	piperylene (10)	3h	1:0.03	62%
i	toluene	C	piperylene (10)	3h	1:0.04	72%
j	toluene	C	piperylene (5)	3h	1:0.05	65%
k	toluene	C	*trans*-stilbene (5)	7h	1:0	74%
l	toluene	C	*trans*-stilbene (1)	4h	1:0.02	77%
m	toluene	C	*trans*-stilbene (0.2)	4h	1:0.02	72%
n	toluene	C	*p*-terphenyl (5)	4h	1:0.13	64%
o	toluene	C	*o*-terphenyl (5)	3h	1:0.13	65%
p	heptane	C	benzophenone (5)	5h	1:0.78	60%
q	heptane	C	benzophenone (10)	5h	1:0.96	64%
r	toluene	C	acetophenone (5)	3h	1:0.71	68%

[a]Lamps with maximum wavelengths are C = 365 nm, B = 300 nm, A = 254 nm.

Results in table 3 showed that hydrocarbon solvents such as heptane and toluene were giving the best compromise between conversion and (*Z*)-selectivity (entries **a** and **d**) compared to halogenated solvents (entry **b**) or ethers (entry **c**). An interesting result was obtained when acetone was used as the solvent (entry **e**). Although not ideal, as it could react with the isocyanide and the carboxylic acid to give a Passerini adduct, it afforded a very good *Z/E* ratio. Irradiation using UV lamps with a maximum at 365 nm was giving better results, compared to shorter wavelengths (entries **f** and **g**), both for *Z/E* ratios and yields. The reactions at 254 or 300 nm were faster, as a consequence of the higher kinetics of the Wolff rearrangement, but also decomposition products could be observed in the crude. In a second set of experiments molecules known to act as photosensitizers or

photoquenchers were added to the reaction mixture. From a general point of view it was observed that when the reaction was performed in the presence of molecules such as piperylene or *trans*-stilbene a higher (*Z*)-selectivity was observed (entries **h**-**m**). On the contrary, photosensitizers such as benzophenone or acetophenone partially reversed the selectivity in favor of the (*E*)-isomer (entries **p**-**r**). Unfortunately, the (*E*)-isomer could not be obtained as the major product, as isomerization reached a stationary state and prolonged irradiation caused partial decomposition of the isomeric mixture. Terphenyl derivatives, although known to be photoquenchers, did not produce appreciable differences (entries **n** and **o**) compared to the reactions without additives. The amount of additive was also important, as its effect increased when increasing the number of equivalents. Using five equivalents of *trans*-stilbene it was possible to obtain selectively the (*Z*)-olefin; however, from a practical point of view, purification of the product in the presence of a large excess of additive could be a problem. Moreover, some additives were only partially soluble in heptane, and therefore toluene was often preferred. The use of piperylene, a low boiling point solvent, was indeed an advantage (using 10 equivalent, the undesired (*E*)-isomer was only 3%), since it could be easily removed by evaporation. Unfortunately, although enquiring various chemical suppliers, we never succeeded to get an affordable price for this compound, and for this reason an extensive use of piperylene was economically unpractical. We therefore moved back to *trans*-stilbene and found that its amount could be reduced to 0.2 equivalents without a detectable loss of selectivity (entry **m**).

As the molecules used as additives in these experiments act as quenchers or sensitizers of triplet excited states, it could be rationalized that the *Z/E* photoisomerization of captodative olefins is proceeding, at least partially, through triplet excited states that could therefore be affected by the presence of substances able to enhance or suppress their formation. On the other hand, the Wolff rearrangement of diazoketones was partially slowed down by the presence of additives, but this effect was observed both with quenchers and sensitizers. This can be explained with the capture of

part of the incident photons by the molecules of additive, independently by their nature. Indeed, the absence of triplet excited states involved in the Wolff rearrangement has been demonstrated.[14]

Development of a flow system for the photochemical reaction

In parallel with the investigation of the effect of quenchers and sensitizers as additives, we also reasoned that a higher level of (*Z*)-selectivity could be obtained if we could reduce the irradiation times. Recently, continuous-flow chemistry has attracted the attention of many research groups, both in academia and industry. In particular, it has been proven effective in photochemical transformations,[15] as the reduced size of reaction channels allows a more efficient penetration of light through the reaction mixture. Moreover, continuous removal of products from the irradiated area can suppress secondary photoreactions, increasing yield and purity of the desired products. Many examples of homogeneous and heterogeneous photochemical reactions under flow conditions have been recently described, although to the best of our knowledge there are no examples of multicomponent condensations. We therefore set up an in house flow system made of a syringe pump, a flow reactor assembled by wrapping a FEP tube (Φ = 1.6 mm, length= 2.5m) around a hollow cylinder hanging in the center of the Rayonet cavity, and a collection flask (the assemblage is illustrated in the supporting information). A toluene solution of the three reagents (phenyldiazoketone, butylisocyanide and 3'-methoxyphenylacetic acid) was then syringed in the tube and the elute was analyzed by TLC. After various attempts at different concentrations and elution times, best results were obtained using a 0.034 M solution of reagents and a flow rate of 15 mL/h. Under these conditions, in the absence of additives, formation of the E isomer was almost completely suppressed, paralleling the results obtained in batch conditions in the presence of an additive.

We then moved to compare these two alternative methodologies, in terms of selectivity and yield, with a representative set of compounds, using different diazoketones, isocyanides and carboxylic

acids (at this stage it was decided not to investigate the full scope of the reaction, as this was already done in a precedent work[4]). Results are summarized in Table 4.

Table 4. Comparison of batch and flow conditions in the synthesis of captodative olefins. Method A: batch reaction with 0.2 eq of *trans*-stilbene (conditions *m* of Table 3). Method B: flow reaction (see text for conditions).

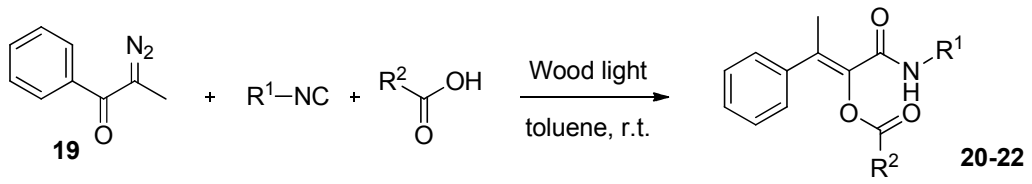
entry	R^1	R^2	R^3	compd.	yield (*Z*)	*Z/E*	method
a	phenyl	*tert*-butyl	3'-MeO-benzyl	**13**	60%	1:0.02	A
b	phenyl	*tert*-butyl	3'-MeO-benzyl	**13**	46%	1:0.03	B
c	4-Cl-phenyl	cyclohexyl	propyl	**15**	78%	1:0	A
d	4-Cl-phenyl	cyclohexyl	propyl	**15**	48%	1:0.05	B
e	benzyl	cyclohexyl	phenyl	**16**	75%	1:0	A
f	benzyl	cyclohexyl	phenyl	**16**	71%	1:0	B
g	3-Cl-propyl	cyclohexyl	penta-1,3-dienyl	**18**	80%	1:0	A
h	3-Cl-propyl	cyclohexyl	penta-1,3-dienyl	**18**	78%	1:0	B

Both approaches afforded captodative olefins almost exclusively as *Z* isomers and in the case of compounds **16** and **18** also yields were comparable (and higher than those obtained with unoptimized conditions reported in Table 2). On the other hand, when aromatic diazoketones were employed, probably due to their higher reactivity, crude NMRs after reactions under continuous flow conditions showed impurities belonging to products of decomposition of ketene, as well as variable amounts of unreacted acid and isocyanide. This resulted in a diminished yield of the multicomponent adducts, as highlighted by the comparison of entry **a** with **b** and entry **c** with **d**. We are currently optimizing the continuous flow apparatus in order to reduce or suppress these side reactions.

Synthesis of tetrasubstituted olefins

Finally, we have investigated the possibility to use our methodology also to synthesize tetrasubstituted olefins by employing disubstituted diazoketones. To this purpose we have prepared compound **19**, according to known procedures,[16] and subjected it to the multicomponent reaction

with an isocyanide and a carboxylic acid under batch conditions. With our delight, compounds **20-22** could be isolated in 54-80% yield as single geometric isomers (Scheme 8). NOE experiments helped to determine the Z configuration of the product.



20: R^1 = *c*Hex, R^2 = Et, yield = 55%
21: R^1 =*c*Hex, R^2 = Bn, yield 80%
22: R^1 = *n*Bu R^2 = Bn, yield 54%

Scheme 8. Synthesis of tetrasubstituted alkenes through the K-3CR approach

Conclusion

2-Acyloxyacrylamides have been employed in the past as substrates for base-mediated rearrangements to pyrrolones and pyrrolidinediones,[6] as well as for the PADAM approach to γ-acylamino-α-oxoamides.[4] These compounds have shown biological activity in various fields as antitumor agents[3] or protease inhibitors.[17] The availability of a straightforward methodology for the obtainment, under batch or flow conditions, of such compounds could open up the route to novel applications. Indeed, we are currently investigating reactions at the double bond such as epoxidations, cyclopropanations and the transition metal catalyzed additions, as well as radical reactions. We will report the results in due course.

Experimental Section

General Experimental Methods. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) and the chemical shifts (δ) are expressed in parts per million relative to tetramethylsylane (TMS) as internal standard (0.00 ppm). Coupling constants are reported in hertz. NMR acquisitions were

performed at 295 K and $CDCl_3$ was used as solvent. HRMS were performed employing an ESI+ ionization method and TOF as analyzer.

Photoinduced reactions were performed with a Rayonet instrument, equipped with 16 lamps (technical features: power 8W, maximum wavelength 365 nm).

Reactions were monitored by TLC. TLC analyses were carried out on silica gel plates (thickness = 0.25 mm), viewed at UV (λ = 254 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4 \cdot 4H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming). Column chromatography was performed with the "flash" methodology using 220−400 mesh silica. Solvents employed as eluents and for all other routinary operations, as well as anhydrous solvents and all reagents used were purchased from commercial suppliers and employed without any further purification. Diazoketones **8** were prepared from the corresponding acyl chlorides according to Ref. [18], while diazoketone **19** was prepared according to Ref. [16].

General procedure for the preparation of K-3CR adducts. Diazoketone **8** (1.0 eq) and carboxylic acid (1.0 eq) were dissolved in the solvent (5mL/0.35mmol) within a glass test tube and degassed under argon atmosphere. The isocyanide (1.0 eq) and the additive (no additive in the case of compound **7**) were added and the solution irradiated at 365 nm under magnetic stirring for three to five hours. The reaction was monitored by TLC: when completed, volatiles were removed under reduced pressure and the crude product purified by means of flash chromatography to afford adducts **7a/7b**, **9-18** and **20-22**.

Mixture of (Z)- and (E)- 3-(cyclohexylamino)-3-oxo-1-phenylprop-1-en-2-yl propionate (7a/7b). Yellow oil (67 mg, 65% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:5.5). Rf = 0.33 (DCM/EtOAc/PE 1:1:5.5). ^{1}H NMR δ 7.50 - 7.47 [m, 2H], 7.37 - 7.27 [m, 3H], 7.16 [s, 0.83H], 6.65 [s, 0.17H], 5.84 [d br, *J* = 8.1, 0.83H], 5.47 [d br, *J* = 8.1, 0.17H], 3.92 - 3.65 [m, 1H], 2.60 [q, *J* = 7.5, 1.66H], 2.55 [q, *J* = 7.5, 0.34H], 2.02 - 1.13 [m, 10H], 1.24 [t, *J* = 7.5,

2.49H], 1.23 [t, *J* = 7.5, 0.51H]. ^{13}C NMR δ 173.2 (**7b**), 171.5 (**7a**), 161.9 (**7a**), 161.5 (**7b**), 142.9 (**7b**), 140.2 (**7a**), 132.6 (**7a**), 132.3 (**7b**), 129.5 (**7a/7b**), 129.1 (**7a/7b**), 128.7 (**7a/7b**), 122.9 (**7a**), 122.4 (**7b**), 48.6 (**7a**), 48.3 (**7b**), 33.0 (**7a**), 32.3 (**7b**), 27.7 (**7a**), 27.3 (**7b**), 25.5 (**7a**), 25.2 (**7b**), 24.8 (**7a**), 24.6 (**7b**), 9.1 (**7a**) 9.0 (**7b**). HR-MS (**7a**) found: [M+H]+ 302.1756; $C_{18}H_{24}NO_3$ requires 302.1756.

(*Z*)-3-(cyclohexylamino)-3-oxo-1-phenylprop-1-en-2-yl benzoate (9). White solid (86 mg, 72% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:5.5), m.p.: 163.7-165.2 °C. Rf = 0.34 (DCM/EtOAc/PE 1:1:5.5). ^{1}H NMR δ 8.19 [dd, *J*= 8.4, 1.5, 2H], 7.68 [tt, *J* = 7.5, 1.2, 1H], 7.56 - 7.50 [m, 4H], 7.33 [s, 1H], 7.28 - 7.24 [m, 3H], 6.03 [d br, *J* = 8.0, 1H], 3.94 - 3.81 [m, 1H], 1.97-1.09 [m, 10H]. ^{13}C NMR δ 163.7, 161.7, 140.0, 134.3, 132.5, 130.3, 129.6, 129.1, 129.0, 128.7, 128.4, 123.6, 48.6, 32.9, 25.5, 24.8. HR-MS found: $[M+H]^+$ 350.1757; $C_{22}H_{24}NO_3$ requires 350.1756.

(*Z*)-3-(cyclohexylamino)-3-oxo-1-phenylprop-1-en-2-yl 2-(3-methoxyphenyl)acetate (10). White solid (100 mg, 75% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:5.5), m.p.: 89.0-91.2 °C. Rf = 0.27 (DCM/EtOAc/PE 1:1:5.5). ^{1}H NMR δ 7.43 - 7.25 [m, 7H], 7.00 - 6.89 [m, 3H], 5.46 [d br, *J* = 8.4, 1H], 3.80 [s, 3H], 3.79 [s, 2H], 3.76 - 3.65 [m,1H], 1.77 - 0.73 [m, 10H]. ^{13}C NMR δ 167.7, 161.2, 160.2, 139.4, 134.2, 132.5, 130.4, 129.6, 129.2, 128.7, 124.0, 121.7, 115.0, 113.4, 55.3, 48.2, 41.9, 32.7, 25.5, 24.9. HR-MS found: $[M+H]^+$ 394.2012; $C_{24}H_{28}NO_4$ requires 394.2018.

(*Z*)-3-(cyclohexylamino)-3-oxo-1-(thiophen-2-yl)prop-1-en-2-yl benzoate (11). Brown solid (43 mg, 37% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:5.5), m.p.: 129.5-131.5 °C. Rf = 0.32 (DCM/EtOAc/PE 2:1:7). ^{1}H NMR δ 8.29 [dd, *J* = 8.4, 1.5, 2H], 7.72 [tt, *J* = 7.5, 1.5, 1H], 7.64 [s, 1H], 7.58 [tt, *J* = 7.8, 1.5, 2H], 7.33 [dt, *J* = 5.1, 1.2, 1H], 7.28 - 7.27 [m, 1H], 7.02 [dd, *J* = 5.1, 3.7, 1H], 5.80 [d br, *J* = 7.8, 1H], 3.95 - 3.82 [m, 1H], 1.97 - 1.07 [m, 10H]. ^{13}C NMR

δ 163.9, 161.3, 137.9, 134.9, 134.4, 131.7, 130.7, 129.5, 129.0, 128.6, 127.2, 118.2, 48.7, 33.0, 25.6, 24.8. HR-MS found: $[M+H]^+$ 356.1322; $C_{20}H_{22}NO_3S$ requires 356.1320.

(*Z*)-3-(butylamino)-3-oxo-1-phenylprop-1-en-2-yl 2-(3-methoxyphenyl)acetate (*Z*-12). Yellow oil (70 mg, 56% yield) upon flash chromatography (silica gel, EtOAc/PE 3:7). Rf = 0.27 (EtOAc/PE 3:7). ^{1}H NMR δ 7.43 - 7.29 [m, 7H], 7.00 - 6.89 [m, 3H], 5.52 [t br, *J* = 5.1, 1H], 3.81 [m, 5H], 3.13 [q, *J* = 6.9, 2H], 1.33 - 1.14 [m, 4H], 0.88 [t, *J* = 6.9, 3H]. ^{13}C NMR δ 167.8, 162.3, 160.3, 139.4, 134.2, 132.5, 130.4, 129.6, 129.3, 128.8, 124.2, 121.7, 115.0, 113.6, 55.4, 42.0, 39.6, 31.5, 20.1, 13.9. HR-MS found: $[M+H]^+$ 368.1852; $C_{22}H_{26}NO_4$ requires 368.1862.

(*E*)-3-(butylamino)-3-oxo-1-phenylprop-1-en-2-yl 2-(3-methoxyphenyl)acetate (*E*-12). Obtained according to entry *q* of Table 3.Yellow oil (30 mg, 24% yield) upon flash chromatography (silica gel, EtOAc/PE 3:7). Rf = 0.36 (EtOAc/PE 3:7). ^{1}H NMR δ 7.50 - 7.20 [m, 6H], 7.00 - 6.75 [m, 3H], 6.64 [s, 1H], 5.53 [s br, 1H], 3.82 [s, 3H], 3.81 [s, 2H], 3.13 [dt, *J* = 6.9, 6.0, 2H], 1.33 - 1.14 [m, 4H], 0.80 [t, *J* = 7.2, 3H]. ^{13}C NMR δ 170.1, 162.2, 159.9, 142.0, 134.6, 132.2, 129.9, 129.2, 128.7, 128.6, 124.0, 121.8, 115.0, 113.2, 55.4, 41.0, 39.3, 30.9, 20.0, 13.8. HR-MS found: $[M+H]^+$ 368.1852; $C_{22}H_{26}NO_4$ requires 368.1862.

(*Z*)-3-(tert-butylamino)-3-oxo-1-phenylprop-1-en-2-yl 2-(3-methoxyphenyl)acetate (13). White solid (70 mg, 56% yield) upon flash chromatography (silica gel, PE/Et_2O 7:3), m.p.: 103.5-105.1 °C. Rf = 0.36 (PE/Et_2O 1:1).^{1}H NMR δ 7.41- 7.26 [m, 6H], 7.22 [s, 1H], 6.99 - 6.86 [m, 3H], 5.49 [s, 1H], 3.80 [s, 3H], 3.78 [s, 2H], 1.22 [s, 9H]. ^{13}C NMR δ 167.8, 161.5, 160.2, 140.1, 134.1, 132.6, 130.3, 129.5, 129.1, 128.8, 123.2, 121.7, 115.0, 113.5, 55.4, 51.4, 41.9, 28.5. HR-MS found: $[M+H]^+$ 368.1864; $C_{22}H_{26}NO_4$ requires 368.1862.

(*Z*)-1-(4-chlorophenyl)-3-((2,2-dimethoxyethyl)amino)-3-oxoprop-1-en-2-yl butyrate (14). White solid (58 mg, 59% yield) upon flash chromatography (silica gel, from PE/Et_2O 1:1 to PE/EtOAc 3:7), m.p.: 85.1-86.8°C. Rf = 0.43 (PE/EtOAc 1:1). ^{1}H NMR δ 7.46 - 7.41 [m, 2H], 7.35

- 7.31 [m, 2H], 7.18 [s, 1H], 6.21 [t br, *J* = 5.6, 1H], 4.41 [t, *J* = 5.3, 1H], 3.50 [t, *J* = 5.6, 2H], 3.42 [s, 6H], 2.55 [t, *J* = 7.4, 2H], 1.75 [sest, *J* = 7.4, 2H], 1.01 [t, *J* = 7.4, 3H]. ^{13}C NMR δ 170.5, 162.7, 140.1, 135.2, 131.0, 130.8, 129.1, 122.7, 102.6, 54.8, 41.4, 36.1, 18.3, 13.8. HR-MS found: $[M+H]^+$ 356.1265; $C_{17}H_{23}ClNO_5$ requires 356.1265.

(*Z*)-1-(4-chlorophenyl)-3-(cyclohexylamino)-3-oxoprop-1-en-2-yl butyrate (15). White solid (76 mg, 78% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:2:8.5), m.p.: 126.0-127.5 °C. Rf = 0.55 (PE/EtOAc 7:3). ^{1}H NMR δ 7.44 – 7.31 [m, 4H], 7.13 [s, 1H], 5.83 [d br, *J* = 7.9, 1H], 3.92-3.79 [m, 1H], 2.54 [t, *J* = 7.3, 2H], 2.00-1.94 [m, 2H], 1.81-1.60 [m, 6H], 1.47-1.34 [m, 2H], 1.26-1.11 [m, 2H], 1.01 [t, *J* = 7.4, 3H]. ^{13}C NMR δ 170.4, 161.7, 140.6, 134.9, 131.2, 130.7, 129.0, 121.9, 48.7, 36.1, 33.0, 25.5, 24.8, 18.3, 13.7. HR-MS found: $[M+H]^+$ 350.1520; $C_{19}H_{25}ClNO_3$ requires 350.1523.

(*Z*)-1-(cyclohexylamino)-1-oxo-4-phenylbut-2-en-2-yl benzoate (16). White solid (74 mg, 55% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:5.5), m.p.: 125.5-126.3 °C. Rf = 0.44 (DCM/EtOAc/PE 1:1:5.5). ^{1}H NMR δ 8.17 [dd, *J* = 8.2, 1.1, 2H], 7.67 [tt, *J* = 7.4, 1.2, 1H], 7.53 [t, *J* = 7.6, 2H], 7.31 - 7.18 [m, 5H], 6.68 [t, *J* = 7.6, 1H], 5.84 [d *br*, *J* = 8.0, 1H], 3.89 - 3.77 [m, 1H], 3.44 [d, *J* = 7.6, 2H], 1.94 - 1.05 [m, 10H]. ^{13}C NMR δ 163.9, 161.0, 141.3, 138.1, 134.3, 130.4, 128.9, 128.7, 128.7, 128.4, 126.7, 125.5, 48.5, 33.0, 32.5, 25.5, 24.8. HR-MS found: $[M+H]^+$ 364.1909; $C_{23}H_{26}NO_3$ requires 364.1913.

(*Z*)-1-(cyclohexylamino)-1-oxo-4-phenylbut-2-en-2-yl 2-(3-methoxyphenyl)acetate (17). Yellow oil (78 mg, 62% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1.5:5). Rf = 0.61 (DCM/EtOAc/PE 1:2:4.5). ^{1}H NMR δ 7.34 - 7.14 [m, 6H], 6.99 - 6.86 [m, 3H], 6.64 [t, *J* = 7.6, 1H], 5.31 [d br, *J* = 8.2, 1H], 3.80 [s, 3H], 3.75 [s, 2H], 3.71 - 3.59 [m, 1H], 3.34 [d, *J* = 7.6, 2H], 1.72 - 0.69 [m, 10H]. ^{13}C NMR δ 168.0, 160.5, 160.2, 140.5, 138.0, 134.6, 130.4, 128.7, 126.6, 125.9, 121.6, 115.0, 113.3, 55.3, 48.0, 41.6, 32.7, 32.4, 25.5, 24.9. HR-MS found: $[M+H]^+$ 408.2180; $C_{25}H_{30}NO_4$ requires 408.2175.

(*2E*,*4E*)-(*Z*)-6-chloro-1-(cyclohexylamino)-1-oxohex-2-en-2-yl hexa-2,4-dienoate (18). Yellow oil (15 mg, 43% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:6). Rf = 0.22 (DCM/EtOAc/PE 1:1:6). ^{1}H NMR δ 7.49 - 7.40 [m, 1H], 6.47 [t, *J* = 7.7, 1H], 6.36 - 6.22 [m, 2H], 5.92 [d, *J* = 14.8, 1H], 5.75 [d *br*, *J* = 7.8, 1H], 3.87 - 3.74 [m, 1H], 3.53 [t, *J* = 6.4, 2H], 2.21 [m, 2H], 1.95 - 1.86 [m, 7H], 1.70 - 1.07 [m, 8H]. ^{13}C NMR δ 164.2, 160.9, 148.3, 142.1, 141.5, 129.6, 125.3, 116.4, 48.3, 44.3, 33.0, 31.0, 25.6, 24.8, 23.4, 18.9. HR-MS found: $[M+H]^+$ 340.1678; $C_{18}H_{27}ClNO_3$ requires 340.1679.

(*Z*)-1-(cyclohexylamino)-1-oxo-3-phenylbut-2-en-2-yl propionate (20). White foam (80 mg, 55% yield) upon flash chromatography (silica gel, PE/EtOAc 8:2). Rf = 0.36 (PE/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.17 [m, 5H], 5.93 (d br, *J* = 7.7, 1H), 3.92 - 3.80 [m, 1H], 2.40 [s, 3H], 2.16 [q, *J* = 7.6, 2H], 1.98 - 1.93 [m, 2H], 1.74 - 1.59 [m, 2H], 1.47 - 1.12 [m, 6H], 0.93 [t, *J* = 7.6, 3H]. ^{13}C NMR δ 172. 9, 162.7, 139.7, 136.3, 135.3, 128.3, 127.7, 127.2, 48.1, 33.0, 27.4, 25.6, 24.8, 19.8, 8.9. HR-MS found: $[M+H]^+$ 316.1919; $C_{19}H_{26}NO_3$ requires 316.1913.

(*Z*)-1-(cyclohexylamino)-1-oxo-3-phenylbut-2-en-2-yl 2-phenylacetate (21). White solid (75 mg, 75% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:5.5), m.p.: 124.0 - 125.4 °C. Rf = 0.42 (PE/EtOAc 8:2). ^{1}H NMR δ 7.33 - 7.28 [m, 6H], 7.21 - 7.13 [m, 4H], 5.45 [d br, *J* = 8.0, 1H], 3.77 - 3.64 [m, 1H], 3.41 [s, 2H], 2.45 [s, 3H], 1.77 - 1.71 [m, 2H], 1.64 - 1.52 [m, 2H], 1.36 - 1.20 [m, 2H], 1.13 - 0.99 [m, 2H], 0.86 - 0.73 [m, 2H]. ^{13}C NMR δ 169.2, 162.1, 139.9, 137.0, 135.5, 133.0, 129.3, 129.1, 128.3, 127.8, 127.6, 127.2, 47.9, 41.2, 32.7, 25. 6, 24.9, 19.9. HR-MS found: $[M+H]^+$ 378.2076; $C_{24}H_{28}NO_3$ requires 378.2069.

(*Z*)-1-(butylamino)-1-oxo-3-phenylbut-2-en-2-yl 2-phenylacetate (22). White solid (65 mg, 54% yield) upon flash chromatography (silica gel, DCM/EtOAc/PE 1:1:5.5), m.p.: 72.3 - 73.4 °C. Rf = 0.34 (DCM/EtOAc/PE 1:1:5.5). ^{1}H NMR δ 7.35 - 7.11 [m, 10H], 5.56 [t br, *J* = 6.0, 1H], 3.42 [s, 2H], 3.12 [dt, *J* = 6.9, 6.0, 2H], 2.46 [s, 3H], 1.32 - 1.14 [m, 4H], 0.87 [t, *J* = 7.0, 3H]. ^{13}C NMR δ

169.3, 163.0, 139.8, 137.3, 135.4, 132.9, 129.2, 129.0, 128.3, 127.8, 127.6, 127.1, 41.2, 39.0, 31.4, 20.1, 20.0, 13.8. HR-MS found: $[M+H]^+$ 352.1919; $C_{22}H_{26}NO_3$ requires 352.1913.

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Supporting Information availability statement

Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **7**, **9-18** and **20-22**. Set up of the flow apparatus and emission spectra of UV lamps. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Footnotes

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