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Ketene 3-Component Staudinger Reaction (K-3CSR) to β-Lactams: A New Entry in the Class of Photoinduced Multicomponent Reactions

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Dedicated to Prof. Ferenc Fülöp in occasion of his 70th birthday.

The Staudinger synthesis of β-lactams from imines and ketenes has been conducted photochemically only in very limited cases. Recent advances in the visible light mediated Wolff rearrangement of diazoketones allowed us to perform, for the first time, a 3-component Staudinger reaction, by mixing aldehydes, amines and diazoketones in the dark and switching the light on after imine formation. The new photoinduced reaction parallels the classic methods in terms of efficiency/selectivity and adds to the existing multicomponent approaches for the preparation of combinatorial libraries of compounds. A thorough optimization of the reaction conditions was performed both for the *classic* two component reaction and for the novel three component version of the photoinduced Staudinger reaction.

The Staudinger synthesis is a well-known thermal $[2+2]$ cyclo-addition of ketenes and imines, extensively used to assemble β-lactams heterocycles; the success of this reaction is due to its versatility and selectivity.[1] The widely accepted mechanism is stepwise and involves the nucleophilic attack of the imine to the ketene, followed by a conrotatory electrocyclic ring closure of the zwitterionic intermediate.[2] Although the multicomponent synthesis of β-lactams, exploiting the Ugi reaction, has been already reported several times,[3] to the best of our knowledge the Staudinger synthesis has never been converted into a three component reaction between ketenes, amines and carbonyl derivatives, probably due to the intrinsic reactivity of ketenes and acyl chlorides (the typical ketene precursors) with amines.
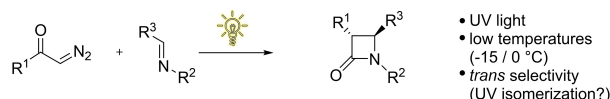
Due to our ongoing interest in the generation of ketenes through the photochemical Wolff rearrangement of

diazoketones,[4] and to our recent discovery that Blue LEDs can be used as an alternative to UV radiation,[5] we decided to apply this approach for the synthesis of β-lactams. Surprisingly, by searching the relevant literature, we have found only the reports by Podlech[6] and Xu,[7] in which ketenes were prepared in situ from diazoketones using UV radiation, and reacted with imines at low temperatures. Xu compared also the photochemical and thermal (microwave) Staudinger reaction, concluding that the UV-mediated reaction often produced by-products, while the microwave-assisted reaction was more efficient, convenient, and practical.[7a]
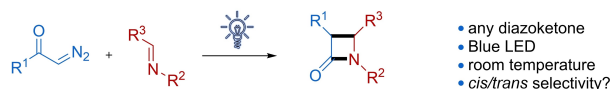
Very recently Glorius reported an alternative photochemical approach based on the degradation of α-ketosilanes, in turn reacted with preformed imines.[8]

Considering these results, we have identified a gap in the literature, that could be filled by using visible light to induce the Wolff rearrangement and by performing the rection as a three-component condensation (Figure 1). In addition, Podlech[6e] and Xu[7a] initially justified the observed trans selectivity as a result of UV-mediated isomerization of the imine, and a note in the manuscript by Podlech ("*Unfortunately a photochemically induced degradation/rearrangement of the diazoketones (Wolff rearrangement) without isomerization of the imines is not possible, since the absorption maxima of both compounds are in the region of 250 nm.*") caught our attention. We decided to reproduce the reaction first reported by Podlech
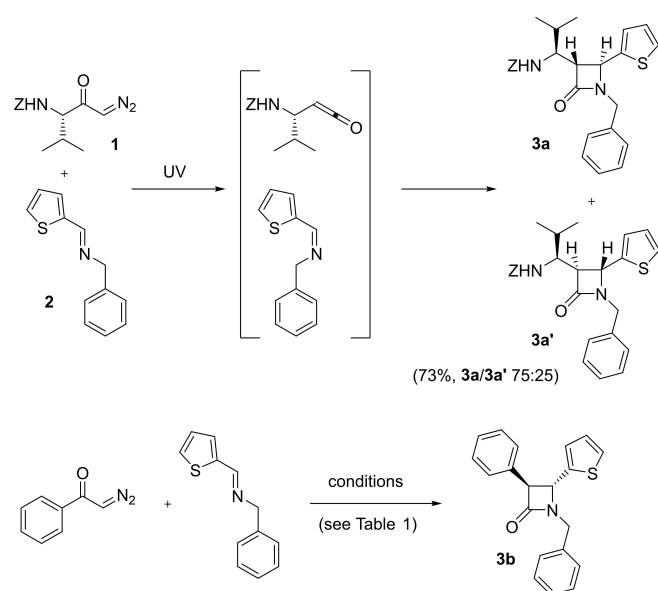
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Figure 1. State of the art and present work on the photoinduced Staudinger synthesis of β-lactams.

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and depicted in Scheme 1 (top) using Blue LEDs instead of UV radiation, expecting to find a different selectivity. Conditions were initially kept the same, therefore 2 equivalents of imine **2** were used in respect to the diazoketone **1**, diethylether was used as the solvent and the temperature was set to −15 °C. The product was isolated solely as the *trans* isomer, as a 3 : 1 mixture of diastereoisomers **3a** and **3a′**, paralleling the results obtained by Podlech and ruling out he hypothesis that selectivity was

due to UV-mediated isomerization of the imine. Yield, however, was modest (25 %), and the same reaction was therefore tested at room temperature. Alongside an unchanged selectivity, in this case the isolated yield was 74 % (lit. 73 %).

With these intriguing results in hand, a thorough optimization of the reaction conditions was undertaken. To the best of our knowledge, such study has never been performed before.[9] A model reaction between imine **2** and phenyldiazoketone (instead of **1**) was chosen to reduce the stereochemical complexity of the crude mixture and allow faster yield determination by NMR using an internal standard (Scheme 1, bottom). The results of the optimization study are reported in Table 1. The *trans* isomer **3b** was obtained in all cases. Interestingly, DCM (*entry 2*) performed much better than the other solvents tested (entries 1, 3–6). It has been reported that halogenated solvents are not totally inert in UV-photoinduced reactions,[10] and their cut-off is close to 250 nm; on the other hand, under visible light, dichloromethane can be effectively employed in photochemical reactions. The use of a less energetic radiation was found crucial, as reactions irradiated at 405, 385 and 365 nm performed worse (entries 7–9). The molar ratio of the imine in respect to the diazoketone (entries 10–11) or the reaction concentration (entries 13–14) had almost no influence, although better results were obtained using the diazoketone in excess (entry 12). This latter option, however, was discarded for subsequent studies as diazoketone is usually the most valuable reagent. The use of an internal standard for yield determination was found very time-efficient, as the reaction optimization could be carried out in few days, and values were consistent with the isolated yields after column chromatography, when these latter were determined.

Having established the optimized conditions, we moved to investigate the scope of the reaction using different diazoketones and imines. The compounds synthetized by this procedure are shown in Figure 2. All compounds were obtained solely as the *trans* isomer in moderate to good yields. Aliphatic and differently-substituted aromatic diazoketones performed similarly. As previously reported,[6e] aliphatic aldehydes did not afford any product.

It is worth noting that most of the β-lactam structures synthetized in this work are unprecedented, apart from compound **3g** and **3i**. Compound **3g** was either synthetized via a classical Staudinger reaction from phenylacetyl chloride, and obtained selectively as the trans isomer,[11] or from a phenylacetyl thioester in the presence of TiCl₄, and obtained as a trans/cis mixture.[12] Compound **3i**, on the other hand, was obtained from phenyldiazoketone under MW heating, and obtained again as a trans/cis mixture.[13] In addition, Xu, on similar compounds obtained through a thermal Wolff rearrangement, observed a decrease in *trans* selectivity by switching from benzylamine to isopropylamine,[14] whereas in our case compounds **3g** and **3i** were obtained exclusively as the trans isomer. The present methodology appears, therefore, to be more selective than the existing ones.

As previously discussed, the Staudinger reaction has never been performed as a three-component reaction; the methodology reported in this work is in principle compatible with a

Scheme 1. Reaction of diazoketone **1** and imine **2** under UV irradiation (top). Reaction of phenyldiazoketone with imine **2** under different conditions (bottom).

Table 1. Optimization of the Staudinger reaction between phenyldiazoketone and imine **2**.

Entry[a]	Solvent	Equivalents[b]	Wavelength[c]	Yield (**3b**)
1	Et₂O	2	450	32 %[d]
2	DCM	2	450	65 %[d]
3	acetonitrile	2	450	40 %[d]
4	HC(OMe)₃	2	450	34 %[d]
5	THF	2	450	30 %[d]
6	MeOH	2	450	3 %[d]
7	DCM	2	405	25 %[d]
8	DCM	2	385	23 %[d]
9	DCM	2	365	30 %[d]
10	DCM	1.5	450	64 %[d] **75 %[e]**
11	DCM	1	450	62 %[d]
12	DCM[f]	0.5	450	75 %[d]
13	DCM[g]	2	450	60 %[d]
14	DCM[h]	2	450	55 %[d]

[a] Reactions were performed dissolving phenyldiazoketone (0.09 mmol) and imine **2** in the given solvent (3 mL, 0.03 M) and irradiating the resulting solution at the given wavelength for 24 h. [b] Equivalents of imine **2** referred to the moles of phenyldiazoketone (in the case of entry 12 the amount of phenyldiazoketone used was 0.18 mmol). [c] Details on the photochemical equipment are given in the supporting information. [d] Yield determined by NMR using DMSO as internal standard. [e] Reaction performed on 0.18 mmol of diazoketone, isolated yield after column chromatography. In this case NMR yield was 73 %. [f] 0.18 mmol of diazoketone were used. [g] The reaction was performed at 0.015 M concentration. [h] The reaction was performed at 0.06 M concentration.
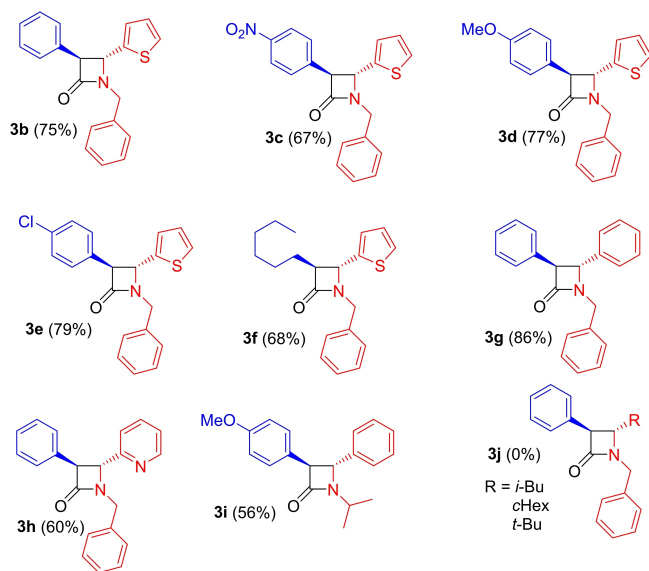
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Figure 2. Scope of the Staudinger reaction between various diazoketones and imines (in brackets isolated yields after column chromatography).

multicomponent approach, since diazoketones are inert towards aldehydes and amines. Only after formation of the imine from these latter reagents, the activation of diazoketones can be initiated by switching the light on. With this idea in mind, we moved to optimize the conditions of the three-component reaction between phenyldiazoketone, benzylamine and 2-thiophene carboxaldehyde. In all tests the molar ratio was kept 1:1:2. The excess of aldehyde was used to shift the equilibrium of the imine formation, as aldehydes are inert towards ketenes, but amines are not. As outlined in Table 2, again dichloromethane performed much better that ethereal solvents (*entry 3*) and trimethyl orthoformate (*entry 2*). Addition of Al$_2$O$_3$ resulted crucial to push the equilibrium towards the formation of the imine, as the amount of N-benzyl phenylacetamide, derived from the reaction of the ketene with benzylamine, was reduced from 30% (*entry 1*) to less than 5% (*entry 4*). In heterogeneous reactions the incident radiation can be scattered and reflected

Table 2. Optimization of the Ketene 3-Component Staudinger Reaction.

Entry[a]	Solvent	Time[b]	Additive	Yield
1	DCM	24 h	–	30%[c]
2	HC(OMe)$_3$	24 h	–	n.d.[c]
3	THF	24 h	–	3%[c]
4	DCM	24 h	Al$_2$O$_3$[d]	60%[c]
5	DCM	24 h	MS 4 Å[d]	20%[c]
6	DCM	48 h	Al$_2$O$_3$[d]	68%[c], **63%**[f]
7	DCM	24 h	Al$_2$O$_3$[e]	54%[c]

[a] Reactions were performed dissolving phenyldiazoketone (0.09 mmol), benzylamine (0.09 mmol) and 2-thiophenecarboxaldehyde (0.18 mmol) in the given solvent (3 mL, 0.03 M) and stirring the solution in the dark for the given time. The solution was then irradiated at 450 nm for 24 h. [b] Time after which irradiation started. [c] Yield determined by NMR using DMSO as internal standard. [d] 15 mg added to the solution. [e] 30 mg added to the solution. [f] Reaction performed on 0.18 mmol of diazoketone and amine, isolated yield after column chromatography.

Table 3. Comparison of isolated yields for products **3b–3g** obtained by standard 2-CR and novel K-3CSR.

product	2-CR	K-3CSR	product	2-CR	K-3CSR
3b	75%	63%	**3f**	68%	51% (46%)[a]
3c	67%	46%	**3g**	86%	54%
3d	77%	64%	**3h**	60%	49%
3e	79%	71%	**3i**	56%	45%

[a] The reaction was performed with a molar ratio 1:1.5:2 between diazoketone, amine and aldehyde.

by solid particles,[15] but in this case the use of a small amount of solid Al$_2$O$_3$ seemed not to be a problem. Molecular sieves did not have the same beneficial effect (*entry 5*). Slight improvement was observed when the reaction was kept in the dark for prolonged time (*entry 6*), but not when a larger amount of Al$_2$O$_3$ was used (*entry 7*). Under optimized conditions the reaction performed similarly to the standard two-component fashion.

Gratified by these results, we moved to synthetize the compounds of Figure 2, through this novel three-component approach, and compared the results with those obtained with the standard Staudinger conditions (Table 3). The isolated yields of the products obtained through the three-component reaction are somewhat lower than those of the reactions with preformed imines, this may be partly due to the incomplete formation of the imine itself, or to the presence of solid Al$_2$O$_3$ in the reaction environment. The lower yields, however, are compensated for by the greater synthetic simplicity and the possibility of transferring the process to an automated system for library generation.

In conclusion, we have reported for the first time a general, visible-light photoinduced three component Staudinger β-lactam synthesis, where diazoketones, amines and aldehydes are mixed all in once. Although the Staudinger reaction is more than a hundred years old, no-one had previously attempted to generate imines *in situ*, as is the case, for example, of the most famous multicomponent reaction, the Ugi reaction. Moreover, thanks to a thorough optimization of both the 2- and 3-CR, we have demonstrated that dichloromethane performs much better than other solvents and that the observed *trans* selectivity is probably a consequence of a slow zwitterionic intermediate ring closure, as later proposed by Xu,[7b,14] and not of UV-mediated imine isomerization, as previously proposed by Podlech.[6e]

This novel Ketene 3-Component Staudinger Reaction (K-3CSR) adds on the already reported K-3CR[4a] and SK-3CR[4d] and further demonstrates the versatility of photoinduced multi-component reactions.[16] Combinatorial libraries of β-lactams can be now prepared in a straightforward manner, without preliminary preparation of the imine derivatives, and further developments will be reported in due course.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

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