Synthetic Methods

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Ketene Three-Component Reaction: A Metal-Free Multicomponent Approach to Stereodefined Captodative Olefins

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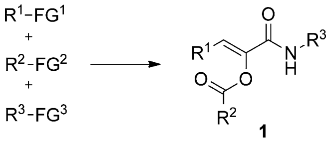
The stereoselective synthesis of polysubstituted alkenes remains one of the most interesting subjects in organic synthesis. Captodative olefins, alkenes with both an electron-withdrawing and an electron-donating group at the α-carbon,[1] have proved to be very versatile synthons for cycloadditions,[2] Friedel–Crafts reactions,[3] and natural product synthesis.[4] Furthermore, the presence of substituents at the β-position strongly modifies both stereo and regioselectivity,[5] thus rendering these compounds particularly appealing. Therefore, straightforward metal-free access to compounds of general formula **1** (Scheme 1) would be highly desirable and add to the limited number of existing methods, which usually require multistep synthesis.[6] Moreover, a multicomponent approach would allow for the introduction of the R substituents through the highly convergent use of simple building blocks.



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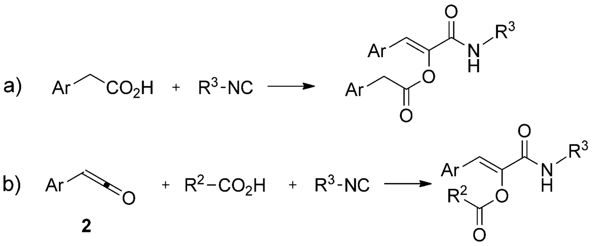
Scheme 1. General multicomponent approach to captodative olefins **1**. FG = functional group.

We have recently discovered that arylacetic acids and isocyanides react at high temperatures to give (*Z*)-α-acyloxy-β-arylacrylamide adducts (**1**; $R^1 = Ar$; $R^2 = R^1{-}CH_2$) incorporating two molecules of acid and one of isocyanide.[7] The key feature of this reaction is that one molecule of carboxylic acid behaves as an electrophile through formation of an acyl imidate with one molecule of isocyanide. Unfortunately, although this new reaction allows easy access to compounds of general formula **1**, R^1 and R^2 cannot be varied independently: we have been unable to obtain an acceptable regioselectivity favoring the multicomponent adduct with a combination of two different arylacetic acids. However, we have reasoned that the same final product **1** could be obtained through a Passerini-like multicomponent reaction where an arylketene **2** ($R^1 = Ar$) replaces the carbonyl component, as in the synthetic pathway illustrated in Scheme 2.



Scheme 2. Comparison between a) the previously reported method[7] and b) the new Passerini-like multicomponent reactions with arylketenes as carbonyl surrogates.

This approach would have the advantage that the structures of the R^1 and R^2 substituents could be chosen independently, thus increasing the diversity of the final adducts.

As a consequence of their high reactivity and low stability, ketenes have rarely been used in multicomponent reactions. Indeed, the few examples available in the literature report the use of 1,1-diphenylketene, which is one of the most stable and more easily isolable.[8] Recently, Ma reported a three component reaction between thiazolium bromides, dimethylacetylenedicarboxylate, and acyl chlorides, where the latter component is used to generate the corresponding ketene in situ.[9] Acyl chlorides, however, are known to react with isocyanides according to the Nef reaction.[10] Moreover, when employing a stoichiometric amount of a base, the ketene could also react with the carboxylic acid and generate an unsymmetrical anhydride side product.

With these considerations in mind, we first decided to examine the shuttle-deprotonation strategy developed by Lectka and co-workers.[11] Phenylketene was generated in situ from phenylacetyl chloride at −78 °C through the use of quinine as a catalytic shuttle base and proton sponge as an insoluble stoichiometric base. After ten minutes, cyclohexyl isocyanide and benzoic acid were added, and the reaction mixture was allowed to warm to room temperature (Scheme 3).

Two products were isolated from the reaction mixture, the main one being the expected multicomponent "hetero" adduct **3** in 71 % yield. The minor product, isolated in 6 % yield, was identified as the "homo" derivative **4**, which incorporates phenylacetic acid as the carboxylic component. Attempts to improve the final outcome, including employing freshly distilled phenylacetyl chloride, molecular sieves, an excess of benzoic acid (up to two equivalents), addition of cyclohexyl isocyanide and benzoic acid at different times, use of various temperatures and solvents, and replacement of the

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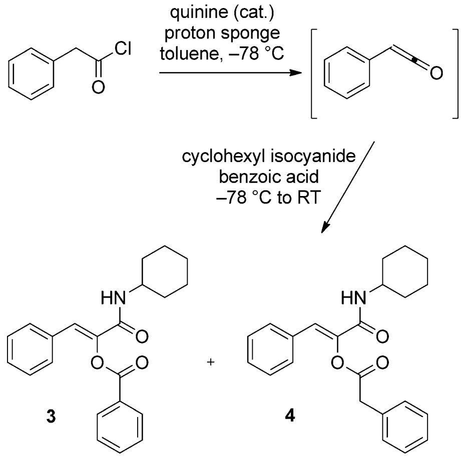


Scheme 3. Ketene three-component reaction using phenylacetyl chloride and shuttle deprotonation.

proton sponge with potassium carbonate,[12] were only partially successful: under the optimized conditions the amount of homo adduct was reduced to 4%. However, when employing other carboxylic acids the results were highly variable and generally disappointing; with propionic acid, for example, the ratio of hetero and homo adducts was 1:0.4, with pivalic acid 1:0.3, and with methoxyacetic acid nearly 1:1.

As previously discussed, a side reaction of this approach is the formation, from one molecule of ketene and one of acid, of an unsymmetrical anhydride; this in turn could react with an additional molecule of acid to generate a symmetrical anhydride and phenylacetic acid, responsible for the formation of the homo adduct. As this process would be favored by the presence of an added base, we looked for alternative methods to generate the ketene that do not require the presence of a base in the reaction medium. First attempts were again carried out using a method developed by Lectka and co-workers:[13] the ketene was generated by passing a solution of phenylacetyl chloride through a short column containing BEMP resin cooled at −78°C, and the resulting base-free solution dripped into a flask containing cyclohexylisocyanide and propionic acid. After several unsuccessful attempts, we eventually isolated the desired hetero adduct with no traces of the homo product. However, the yield was rather low (14%).

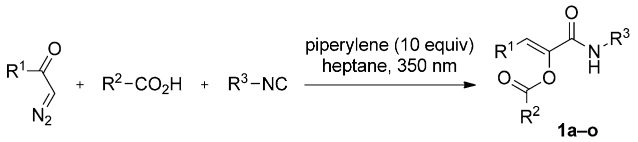
Alternatively, we considered that phenylketene could be generated from 2-diazo-1-phenylethanone through the Wolff rearrangement.[14] Rearrangement may be initiated by thermolysis, photolysis, or metal ion catalysis, the latter two being the more widely employed. As metal catalysis often requires an added base and is less appealing from the point of view of sustainability, we decided to investigate the photolytic three component reaction. In a control experiment we reacted equimolar amounts of 2-diazo-1-phenylethanone, cyclohexylisocyanide, and propionic acid at room temperature in the absence of UV light, and observed that no reaction took place.[15] However, to our delight, when we irradiated the same components in a quartz test tube at 350 nm, the multicomponent adduct was obtained in 50% yield. Variation of the reaction conditions showed that heptane was a better solvent than toluene, diisopropyl ether, or chloroform, and that when using a shorter wavelength (300 or 254 nm) the reaction was faster but less clean, as a consequence of the partial instability of the captodative olefin upon irradiation. The best results were obtained by irradiating the deoxygenated reaction mixture at 350 nm for three hours in the presence of an excess of *trans*-piperylene (Table 1).[16]

Table 1: Optimization of the photoinduced ketene three-component reaction.

Entry	Solvent	λ [nm]	Yield [%]
1	heptane	350	50
2	toluene	350	46
3	chloroform	350	40
4	diisopropyl ether	350	26
5	heptane	300	31
6	heptane	254	21
7	heptane[a]	350	66

[a] Reaction conducted with piperylene (10 equiv) as an additive.

We then moved to explore the scope of the reaction (Scheme 4), and found the method tolerant to aromatic and heteroaromatic diazoketones, as well as aliphatic and aromatic carboxylic acids and isocyanides (Table 2). Yields of



Scheme 4. Photoinduced three-component reaction between diazoketones, carboxylic acids and isocyanides.

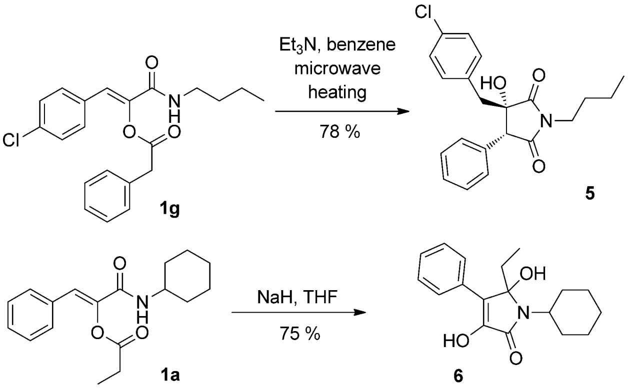
Table 2: Scope of the photoinduced ketene three-component reaction.

Entry	Product	R^1	R^2	R^3	Yield [%][a]
1	**1a**	phenyl	ethyl	cyclohexyl	66
2	**1b**	phenyl	phenyl	cyclohexyl	72
3	**1c**	phenyl	3′-MeO-benzyl	cyclohexyl	79 (62)
4	**1d**	phenyl	3′-MeO-benzyl	2,6-$Me_2C_6H_3$	61
5	**1e**	phenyl	1-pentynyl	*tert*-butyl	68
6	**1f**	4-ClC_6H_4	4′-Cl-benzyl	$MeOCOCH_2$	(56)
7	**1g**	4-ClC_6H_4	benzyl	*n*-butyl	68
8	**1h**	2-thiophenyl	phenyl	cyclohexyl	66
9	**1i**	4-ClC_6H_4	(*E*,*E*)-1,3-pentadienyl	cyclohexyl	92
10	**1j**	2-thiophenyl	$BocNHCH_2$	benzyl	62
11	**1k**	benzyl	phenyl	cyclohexyl	67
12	**1l**	benzyl	3′-MeO-benzyl	cyclohexyl	62
13	**1m**	$BocNHCH(CH_3)$	benzyl	cyclohexyl	57
14	**1n**	3-Cl-propyl	(*E*,*E*)-1,3-pentadienyl	cyclohexyl	43
15	**1o**	3-Ac-propyl	benzyl	cyclohexyl	46

[a] Yields shown are after purification by flash chromatography. Yields in parentheses are after isolation by filtration of the reaction mixture. Ac = acetyl, Boc = *tert*-butoxycarbonyl.

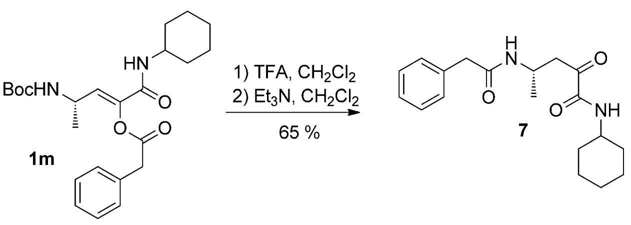
isolated products were generally good, and the final compounds, which were usually purified by flash chromatography, could also be recovered in high purity by simple filtration of the reaction mixture, although with slightly lower yields (entry 3). The results are particularly remarkable when taking into account that ketenes are extremely unstable at room temperature (side reactions can be expected to occur under these conditions) and that equimolar amounts of the reagents are employed. Notably, homo compound **1f**, which decomposed when prepared with our previously developed method,[7] was in this case isolated without problem. Furthermore, carboxylic acids such as 2-hexynoic acid (entry 5), sorbic acid (known to be light sensitive; entry 9) or Boc-glycine (entry 10) could be used without problem.

Pleased by the results obtained with aryldiazoketones, we became interested in extending the approach to alternative diazoketones. It is worth noting that the previously reported method[7] was unsuccessful with acids other than arylacetic ones, and additionally the reaction illustrated in Scheme 3 did not afford any of the desired captodative olefin when acyl chlorides lacking an aromatic ring in the α-position were employed. However, when benzyl diazoketone was irradiated in the presence of benzoic acid and cyclohexyl isocyanide, the desired compound **1k** was isolated in 55% yield; similarly, compound **1l** was obtained in 62% yield. Analogous results were obtained when diazoketones derived from Boc-glycine (entry 13), 4-chlorobutanoic acid (entry 14) and 4-acetylbutanoic acid (entry 15) were employed, thus demonstrating the versatility of this novel photoinduced ketene three-component reaction (K-3CR). Notably, in the case of 3-acetylpropyl diazoketone, no competitive Passerini adduct was observed. Yields were slightly lower than those obtained with aryl diazoketones, probably owing to the higher instability of non-conjugated ketenes and their lower reactivity with isocyanides.[17] Taking into consideration that a plethora of carboxylic acids and isocyanides are now commercially available, and that diazoketones can be easily prepared by the reaction of acyl chlorides[18] or acyl carbonates[19] with diazomethane, the K-3CR can parallel the classical Passerini and Ugi reactions in terms of general application. Moreover, whereas the Passerini and Ugi products afford heterocyclic scaffolds through post-condensation transformations only when additional functional groups are inserted onto the building blocks, we have recently demonstrated that homo captodative olefins, through treatment with base, can rearrange into various pyrrolidines that possess interesting biological activity.[20] To prove that this rearrangement can also take place on the products of the K-3CR, we have treated compound **1g** with Et_3N in benzene under microwave heating, and compound **1a** with NaH in THF, to obtain pyrrolidinedione **5** and dihydropyrrolone **6**, respectively (Scheme 5), thus demonstrating that these heterocyclic compounds are now available in higher diversity and are therefore more useful as probes for exploring the relevant chemical space.



Scheme 5. Base-mediated rearrangement of captodative olefins **1g** and **1a**.

To assess the versatility of our method we have also removed the Boc protection of compound **1m**. Upon neutralization, we observed spontaneous acyl migration, as in the PADAM strategy,[21] and tautomerization to the α-ketoamide **7**. Thus, compared to the classic PADAM approach, the oxo functional group was directly formed with no need for an oxidative step (Scheme 6).



Scheme 6. Application of the PADAM strategy to captodative olefin **1m**. TFA = trifluoroacetic acid.

In conclusion, we have demonstrated that a novel, general, three component reaction can take place between diazoketones, carboxylic acids and isocyanides upon irradiation. The conditions are very mild and the products of this reaction are highly functionalized captodative olefins that can find many applications as versatile synthons in organic synthesis. Compared to Passerini adducts, the additional double bond confers a peculiar reactivity to these molecules, thus K-3CR is not simply a modification of its grandfather P-3CR, but a new multicomponent reaction, with good prospects for reaching the same level of popularity.

Experimental Section

General procedure for the photoactivated multicomponent reaction: Diazoketone (0.35 mmol) was dissolved in heptane (4 mL) in a quartz tube (1 cm diameter) with stirring. Argon was flushed through the solution for 10 min, then carboxylic acid (0.35 mmol), isocyanide (0.35 mmol), and piperylene (3.5 mmol, 0.35 mL) were added, the test tube sealed, and then irradiated while stirring in a Rayonet instrument (16 lamps, 8 W, 350 nm) for 3 h. The precipitate formed was collected by filtration; alternatively solvents were evaporated in vacuo and crude material purified by flash chromatography (ethyl acetate/petroleum ether).

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