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# Toward a Green Atom Economy: Development of a Sustainable Multicomponent Reaction

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**Abstract** The recently discovered photoinduced three-component reaction of diazo ketones, carboxylic acids, and isocyanides can be efficiently performed under continuous-flow conditions with consequential advantages in terms of selectivity and productivity. The investigation of the flow process and the determination of its sustainability are discussed in detail. This multicomponent reaction affords stereodefined captodative olefins, useful as synthons in organic chemistry.

Key words multicomponent reactions, photochemistry, flow chemistry, green chemistry, diazo compounds, isocyanides

The search for efficient and sustainable organic syntheses is a highly topical subject. Multicomponent reactions have been recognized as straightforward processes for diversity-oriented syntheses<sup>1</sup> characterized by high atom economies, limited numbers of synthetic steps, and simplified product-isolation procedures.<sup>2</sup> However, the activation of substrates under mild conditions remains a challenge, particularly when high temperatures are required to overcome energy barriers; various chemical and physical approaches to this problem have been reported.<sup>3</sup> Although photochemistry has only recently been applied to multicomponent reactions, the number of articles published in this interdisciplinary field is increasing rapidly.<sup>4</sup> In general, photoactivated reactions are capable of showing superior selectivity and sustainability to their thermal counterparts.<sup>5</sup>

We recently discovered a new phototriggered multicomponent reaction that we named the ketene threecomponent reaction (K-3CR; Scheme 1). This proceeds under mild conditions upon UV irradiation to give a captodative olefin of general formula I, starting from a diazo ketone II, a carboxylic acid III, and an isocyanide IV.<sup>6</sup>



Scheme 1 General scheme for the ketene three-component reaction (K-3CR)

The key step is a photoinduced Wolff rearrangement of the diazo ketone **II**<sup>7</sup> into a reactive ketene **V** that reacts with **III** and **IV** in a formal Passerini reaction.<sup>7c</sup> The products are useful as synthons in various reactions, including cycloadditions,<sup>8</sup> rearrangements,<sup>9</sup> and radical additions.<sup>10</sup>

When the K-3CR was performed as a batch process in a Rayonet merry-go-round reactor equipped with 16 Wood's lamps (8 W;  $\lambda_{max} = 364$  nm), olefins I were isolated as mixtures of *E*/*Z* geometric isomers in variable amounts.<sup>6b</sup> This was explained as the consequence of competitive light absorption by the generated (*Z*)-captodative olefin and its subsequent isomerization.<sup>11</sup> The use of triplet quenchers such as penta-1,3-diene (piperylene) or *trans*-stilbene was beneficial in suppressing the isomerization. However, the use of these additives in equimolar amount with respect to the reactants and the highly dilute conditions required (up to 0.07 M) resulted in the production of significant amounts of waste.

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Continuous-flow reactors have recently emerged as a promising technology in organic synthesis, especially in photochemistry, where the reduced size of the reaction channels permits efficient penetration of light to the photolyzed solution. This results in a marked reduction in the residence time thereby suppressing the generation of byproducts and, consequently, improving the efficiency and selectivity of the process while permitting an increase in the concentration of the substrate.<sup>12</sup> A preliminary study<sup>6b</sup> of the K-3CR in a photochemical flow reactor incorporating the multilamp reactor used in the batch reactions as a light source showed that the reaction could be performed with a short residence time, thereby suppressing E/Z isomerization of the captodative olefins, even in the absence of a triplet quencher additive. This encouraged us to examine the continuous-flow approach with the aim of optimizing the K-3CR process from the environmental point of view. We assembled a continuous-flow photoreactor consisting of a 12-m-long coil of UV-transparent fluorinated ethylenepropylene polymer (FEP) tubing with an outer diameter of 1.6 mm and an inner diameter of 0.8 mm, wound around a conventional water-cooled photochemical reactor. The light source consisted of a Wood's lamp (16 W), and the capacity of the reactor was 6 mL (Figure 1). The solution was circulated by means of an HPLC pump.



Figure 1 Photograph of the photochemical reactor

We initially focused on optimization of the conditions for the photochemical reaction by examining the reaction shown in Scheme 2, and we investigated the effects of the concentration of the reactants and the flow speed of the solution on the yield and selectivity of this reaction. An equimolar mixture of the three reagents dissolved in toluene (2 mL) was loaded in the injection loop of the HPLC pump. The solution was then pumped through the reaction coil and collected in a flask. The solvent was evaporated under reduced pressure and the crude material was analyzed by NMR spectroscopy to control the consumption of the diazo ketone and to determine the E/Z ratio of the products. The crude product was finally purified by flash chromatography to calculate the isolated yield of the desired product. The results are summarized in Table 1.



Scheme 2 Model reaction used to optimize the process under flow conditions

 
 Table 1
 Optimization of the K-3CR Route to 4a under Continuous-Flow Conditions

Entry	Concentration <sup>a</sup> (M)	Flow rate (mL/h)	Yield⁵ (%)	Z/E
1	0.1	3.6	36	1:0.04
2	0.2	1.8	56	1:0.05
3	0.3	0.6	59	1:0.15
4 <sup>c</sup>	0.1	1.2	-	1:0.10

<sup>a</sup> The concentration refers to that of the diazo ketone. (Equimolar amounts of the diazo ketone, carboxylic acid, and isocyanide were used in argon-equilibrated anhydrous toluene.)

<sup>b</sup> Isolated yield of the Z-isomer;

<sup>c</sup> Isomerization reaction of the (Z)-captodative olefin. Diastereomerically pure (Z)-**4a** was pumped into the flow apparatus and collected after irradiation.

The flow speed was adjusted to achieve almost complete consumption of the diazo ketone. More highly concentrated solutions gave better conversions, probably because the reactive ketene intermediate could interact more easily with the other components; however, because concentrated solutions required longer irradiation times and, consequently, slower flow speeds, they also favored alkene isomerization. The fact that isomerization of the generated captodative olefin (*Z*)-**4a** occurred under our flow conditions was confirmed by irradiating the a solution of the product under similar reaction conditions (Table 1, entry 4). Reducing the flow speed from 3.6 to 1.8 mL/h resulted in only a slight worsening of the isomer ratio (entries 1 and 2),

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the Z-isomer.

whereas increasing the solution concentration from 0.2 to 0.3 M produced only a modest improvement in the yield (entries 2 and 3).

In light of these preliminary results, we decided to carry out a set of photoinduced K-3CRs (Scheme 3). Slight changes in flow and concentration conditions, compared were those shown in Table 1, entry 2 were dictated by the different reactivities of the diazo ketones employed. (Z)-Acyloxyacrylamides 4a-g were obtained in moderate to satisfactory yields in amounts of up to 3.1 g/day (product 4c) and with a Z/E selectivity in excess of 90:10 in all cases.

The results for the synthesis of enamide **4g** (Scheme 4) confirmed the advantages of the continuous-flow photochemical approach over a batch approach in terms of both efficiency and sustainability.

The disappearance quantum yield  $\Phi_{-1}$  for 1-diazo-3phenylacetone has been determined to be 0.26 (a similar value,  $\Phi_{-1}$  = 0.28, was obtained for 2-diazo-1-phenylethanone), and comparable values have been obtained for the Wolff rearrangements of various  $\alpha$ -diazo ketones.<sup>13</sup> We therefore examined the yield, productivity, waste production, and energy expenditure of the reaction. The waste production is well described by the PMI parameter, i.e., the



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Table 2 Performance of Batch and Continuous-Flow Reactors in the K-3CR Reaction for the Synthesis of 4g

Entry	Conditions	Conc. (M)ª	Flow rate (mL/min)	Yield (%) <sup>b</sup>	Productivity (mmol/h)	STY (M/h)	PMI (kg/kg)	Specific productivity (mmol/W × 10 <sup>3</sup> )
1	Batch <sup>c</sup>	0.070	-	75	0.0525	0.0105	39.43	0.410
2	Flow A <sup>d</sup>	0.034	0.25	71	0.362	0.0603	100.7	2.83
3	Flow B <sup>e</sup>	0.078	0.08	58	0.217	0.0361	54.75	13.6
4	Flow B <sup>e</sup>	0.156	0.05	74	0.346	0.0577	23.14	21.6
5	Flow B <sup>e</sup>	0.173	0.03	64	0.199	0.0332	23.30	12.4
6	Flow B <sup>e</sup>	0.234	0.02	78	0.219	0.0365	14.50	13.7

<sup>a</sup> Concentration of the diazo ketone (equimolar amounts of the diazo ketone, carboxylic acid, and isocyanide were used in argon-equilibrated anhydrous toluene).

<sup>b</sup> Isolated yield of the Z-isomer.

<sup>c</sup> The solution (5 mL) was irradiated in a multilamp reactor equipped with 16 × 8 W Wood's lamps ( $\lambda$  = 350 nm).

<sup>d</sup> Flow reactor described in ref. 6b.

<sup>e</sup> Flow reactor described in this work (see above).

total mass of materials required to produce a unit mass of the desired product.<sup>14</sup> The energy expenditure was analyzed by calculating the specific productivity, the number of mmol of product produced for a given amount of energy; in this case, it is the amount of energy consumed by the light source.<sup>15</sup> There are few reports regarding the ecological sustainability of photochemical reactions.<sup>5,15,16</sup>

The use of a batch reactor resulted in a low productivity because of the dilute conditions and the long irradiation time (5 h) that were required (Table 2, entry 1). Furthermore, this process gave an unsatisfactory PMI value and a high energy expenditure. However, changing to continuous-flow conditions did not necessarily improve the process. The use of a nonoptimized photochemical flow reactor<sup>6b</sup> resulted in a highly unsatisfactory PMI (100.7 kg/kg), despite a general improvement in the other parameters [space time yield (STY), productivity, and specific productivity] (entry 2). In this case, a lower concentration of substrate was required to achieve a similar performance to that achieved under batch conditions. With our new photoreactor, however, we were able to use a concentrated solution (up to 0.256 M; entries 3-6). This significantly reduced the amount of waste produced to 14.50 kg/kg (entry 6); it also reduced the energy consumed in the process. The specific productivity increased up to 40 times on changing from a batch reactor to a flow reactor (entries 1 and 4).

As in other photochemical processes discussed in the literature,<sup>15</sup> two issues arise from the assessment of such reactions, namely the highly dilute conditions and the energy supply required to operate the lamps. These are critical points, especially when the reaction has a low quantum yield, as is the case in the photoinduced Wolff rearrangement of diazo ketones **1** that we investigated.

The use of a photochemical flow reactor, with its optimized light absorption, permitted an increase in the concentration of the substrates while maintaining a satisfactory yield and selectivity. This, predictably, resulted in a general reduction in the waste produced (Table 2; PMI). However, the story is somewhat different when we consider the energy supplied. In our case, the use of a highly concentrated solution required a longer irradiation time without any significant improvement in the yield of the reaction. In consequence, the production of the desired product under these conditions involved a greater expenditure of energy, as demonstrated by the specific productivity value (Table 2, entries 5 and 6). We are currently conducting investigations with the aim of further lowering the production of waste while improving the absorption of light by the reaction mixture (for example, by changing from a mesoflow to microflow reactor).<sup>12a</sup>

In conclusion, captodative olefins of general formula **I** have been used as substrates for base-mediated rearrangements to pyrrolones and pyrrolidinediones with antitumor activity.<sup>9</sup> The availability of a straightforward and sustainable method for the production of such compounds could open a route to novel applications that we are currently investigating and will report in due course.

Photoinduced reactions were performed with a Rayonet instrument equipped with up to 16 Wood's light lamps (8 W;  $\lambda_{max}$ : 364 nm), or with the in-house-fabricate flow apparatus described above.

The disappearance quantum yield  $(\Phi_{-1})$  was been measured with a 0.070 mM solution of 1-diazo-3-phenylacetone in toluene on an optical bench equipped with a 150 W high-pressure mercury lamp ( $\lambda_{IRR}$  = 317 nm) with potassium ferrioxalate as actinometer.

Commercially available anhydrous toluene was used as the solvent. All solvents and reagents used were purchased from commercial suppliers and employed without any further purification, apart from the diazo ketones, which were prepared from the corresponding acyl chlorides or mixed anhydrides by the reported procedures. Flash column chromatography was performed on 220–400 mesh silica. NMR spectra were recorded at 300 MHz (<sup>1</sup>H) or 75 MHz (<sup>13</sup>C) on a Varian Mercury-300 spectrometer at 295 K, and the chemical shifts are expressed in ppm relative to TMS as internal standard (0.00 ppm). High-

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resolution mass spectra were recorded on a Waters MicroMass LCT spectrometer, operated in the ESI+ ionization mode, with a TOF ana-3-Phenylacrylate (4e) lyzer.

#### Continuous-Flow Synthesis of Captodative Olefins 4; General Procedure

Equimolar amounts of the diazo ketone, carboxylic acid, and isocyanide were dissolved in anhyd toluene (2 mL) in a test tube, and the solution was flushed with argon for 10 min. The clear solution was loaded into the injection loop of the HPLC system and pumped into the reaction coil (carrier solvent: MeCN) at the preset speed. The solution exiting the reactor was collected in a flask and, when elution was complete, concentrated under vacuum and analyzed by <sup>1</sup>H NMR spectroscopy. The crude material was then purified by flash chromatography (silica gel, PE-EtOAc).

#### (Z)-1-[(Butylamino)carbonyl]-2-(4-chlorophenyl)vinyl Butyrate (4a)

Yellow foam; yield: 72 mg (56%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.42 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.15 (s, 1 H), 6.00 (br s, 1 H), 3.36 (q, J = 7.5 Hz, 2 H), 2.52 (t, J = 7.5 Hz, 2 H), 1.74 (sextet, J = 7.5 Hz, 2 H), 1.58–1.50 (m, 2 H), 1.42– 1.28 (m, 2 H), 1.00 (t, J = 7.5 Hz, 3 H), 0.94 (t, J = 7.5 Hz, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 170.5, 162.6, 140.5, 135.1, 131.2, 130.8, 129.1, 122.2, 39.8, 36.2, 31.8, 20.2, 18.4, 13.9, 13.8.

HRMS: m/z [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>23</sub>ClNO<sub>3</sub>: 324.1361; found: 324.1365.

## (Z)-1-[(tert-Butylamino)carbonyl]-2-phenylvinyl Propionate (4b) White solid; yield: 45 mg (59%); mp 96-97 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.47–7.32 (m, 5 H), 7.12 (s, 1 H), 5.83 (s, 1 H), 2.14 (q, J = 7.8, 2 H), 1.43 (s, 9 H), 1.24 (t, J = 7.5 Hz, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.4, 162.1, 140.8, 132.8, 129.5, 129.1, 128.8, 122.5, 51.7, 28.8, 27.8, 9.1.

HRMS: m/z [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>22</sub>NO<sub>3</sub>: 276.1594; found: 276.1596.

#### (Z)-1-[(tert-Butylamino)carbonyl]-2-phenylvinyl (3-Methoxyphenyl)acetate (4c)

White solid; yield: 86 mg (69%); mp 104–105 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.41–7.26 (m, 6 H), 6.99–6.86 (m, 3 H), 5.49 (s, 1 H), 3.80 (s, 3 H), 3.78 (s, 2 H), 1.22 (s, 9 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 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.

HRMS: *m*/*z* [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>26</sub>NO<sub>4</sub>: 368.1856; found: 368.1864.

#### (Z)-2-(4-Chlorophenyl)-1-[(cyclohexylamino)carbonyl]vinyl Butyrate (4d)

White solid; yield: 49 mg (50%); mp 126-127 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.44–7.31 (m, 4 H), 7.13 (s, 1 H), 5.83 (br d, J = 7.9 Hz, 1 H), 3.92–3.79 (m, 1 H), 2.54 (t, J = 7.3 Hz, 2 H), 2.00– 1.11 (m, 11 H), 1.01 (t, J = 7.4 Hz, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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.

HRMS: m/z [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>25</sub>ClNO<sub>3</sub>: 350.1517; found: 350.1520.

# (1Z)-5-Chloro-1-[(cyclohexylamino)carbonyl]pent-1-en-1-yl (2E)-

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Colorless oil; yield: 78 mg (74%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.82 (d, J = 16.0 Hz, 1 H), 7.58–7.26 (m, 5 H), 6.53 (d, J = 16.0 Hz, 1 H), 5.89 (br d, J = 7.9 Hz, 1 H), 5.74 (t, J = 8.1 Hz, 1 H), 3.82 (m, 1 H), 3.61 (t, J = 6.9 Hz, 2 H), 2.81 (q, J = 7.2 Hz, 2 H), 2.05-1.08 (m, 12 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 164.1, 160.9, 148.0, 141.7, 133.9, 131.2, 129.2, 128.6, 125.4, 115.8, 48.5, 44.3, 33.0, 31.0, 25.6, 24.9, 23.5.

HRMS: m/z [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>27</sub>ClNO<sub>3</sub>: 376.1674; found: 376.1669.

#### (1Z)-3-[(tert-Butoxycarbonyl)amino]-1-[(cyclohexylamino)carbonyl]but-1-en-1-yl Butyrate (4f)

White foam; yield: 34 mg (37%).

<sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  = 7.42 (br d, J = 6.9 Hz, 1 H), 6.63 (br d, J = 6.9 Hz, 1 H), 6.10 (d, J = 8.7 Hz, 1 H), 4.23 (sextet, J = 6.9 Hz, 1 H), 3.57 (m, 1 H), 2.49 (t, J = 7.5 Hz, 2 H), 1.75–1.07 (m, 24 H), 0.95 (t, J = 7.5 Hz, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.0, 161.2, 155.0, 140.6, 127.4, 79.8, 48.5, 43.1, 35.9, 33.1, 32.5, 28.6, 28.5, 25.6, 24.9, 20.7, 18.5, 13.8.

HRMS:  $m/z [M + H]^+$  calcd for  $C_{20}H_{35}N_2O_5$ : 383.2540; found: 383.2537.

#### (1Z)-1-[(Cyclohexylamino)carbonyl]-3-phenylprop-1-en-1-yl Benzoate (4g)

White solid; yield: 133 mg (78%); mp 125–126 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.17 (dd, J = 8.2, 1.1 Hz, 2 H), 7.67 (tt, *I* = 7.4, 1.2 Hz, 1 H), 7.53 (t, *I* = 7.6 Hz, 2 H), 7.31–7.18 (m, 5 H), 6.68 (t, J = 7.6 Hz, 1 H), 5.84 (br d, J = 8.0 Hz, 1 H), 3.89–3.77 (m, 1 H), 3.44 (d, *J* = 7.6 Hz, 2 H), 1.94–1.05 (m, 10 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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. HRMS: *m*/*z* [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>26</sub>NO<sub>3</sub>: 364.1907; found: 364.1909.

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