Heterocycle Synthesis

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Three-Component Synthesis of Ynediones by a Glyoxylation/Stephens–Castro Coupling Sequence**

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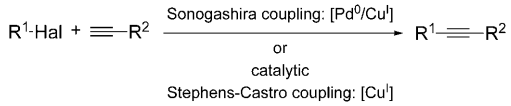
Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday

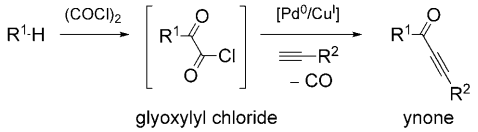
Copper-mediated reactions have been playing an outstanding role in organic chemistry for over a century as manifested in many important transformations and name reactions. Indeed, Ullmann-type reactions can be considered as predecessors of modern cross-couplings. However, copper-mediated transformations have been completely overshadowed by the very dramatic developments in palladium chemistry. Nevertheless, many new remarkable copper-catalyzed processes have appeared in the last decade, thus heralding a renaissance in copper catalysis.[1–5]

In 1963, Stephens and Castro reported a synthesis of diarylacetylenes by a stoichiometric coupling reaction of copper acetylides with aryl iodides, which proceeded in refluxing pyridine under a nitrogen atmosphere.[6] Later, catalytic variants were also developed, some of which allowed milder conditions more tolerant to functional groups.[7] With the advent of the usually more efficient palladium-catalyzed alkynylations[8] and finally the Pd/Cu-catalyzed Sonogashira–Hagihara coupling,[9,10] the Stephens–Castro reaction became far less significant (Scheme 1).



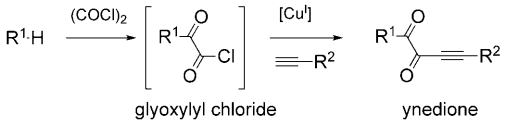
Scheme 1. Sonogashira and catalytic Stephens–Castro alkynylations.

Recently, we reported a new multicomponent approach to alkynones by glyoxylation of electron-rich heterocycles such as indoles and pyrroles with oxalyl chloride under Lewis acid free conditions followed by a novel decarbonylative Sonogashira coupling procedure (Scheme 2).[11]



Scheme 2. Glyoxylation/decarbonylative Sonogashira coupling sequence.

Obviously, if the decarbonylative elimination could be suppressed or excluded, the reaction sequence would lead to the formation of ynediones, highly electrophilic, yet scarcely explored building blocks.[12] The synthesis of 2-oxo-3-butynoates and 2-oxo-3-butynoamides by the Cu-catalyzed coupling of monooxalyl chlorides, described in 2003,[13] was the sole implementation of this intriguing concept. However, prior to our studies, this direct approach was neither extended into a one-pot protocol nor applied to the functionalization of heterocycles. We reasoned that ynediones could be obtained by modifying the glyoxylation/decarbonylative Sonogashira coupling sequence. Possibly, the decarbonylation could be avoided by omitting the Pd precatalyst responsible for the decarbonylative outcome in the coupling step, thus stepping back to the Cu-catalyzed Stephens–Castro reaction (Scheme 3).



Scheme 3. Glyoxylation/Stephens–Castro coupling sequence.

In optimization studies[14] we found that the best results were obtained with 1.0 equivalent of oxalyl chloride, 5 mol% of CuI, 1.0 equivalent of a terminal alkyne, and 3.0 equivalents of triethylamine. In comparison to the corresponding decarbonylative Sonogashira reaction, the coupling step is slower, but essentially complete within 24 h at room temperature. Increasing the reaction temperature diminishes the yield, and prolonged reaction time (48 h) does not increase the yield. The sequence can be performed conveniently on a 5 mmol scale and is preparatively very straightforward (Table 1). The CuI catalyst was obtained from Aldrich (98%) and used as supplied. An ultrapure batch (Alfa Aesar Puratronic, 99.999% (metals basis)) gave the same yield, thus proving that copper is indeed the catalytically

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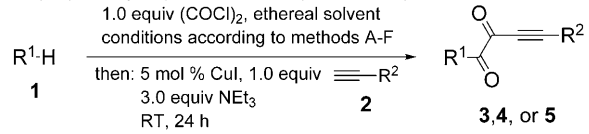
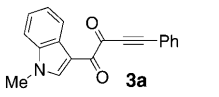
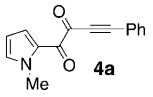
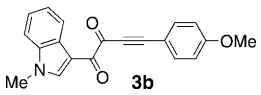
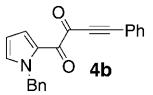
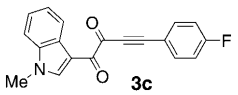
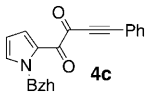
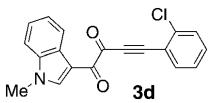
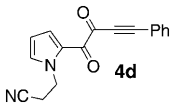
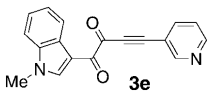
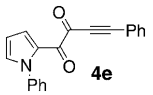
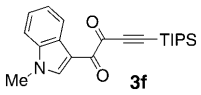
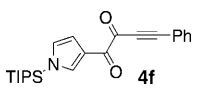
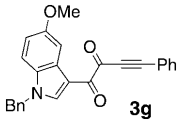
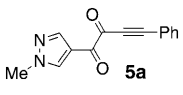
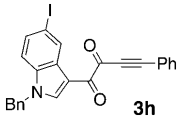
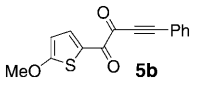
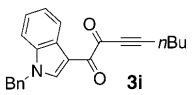
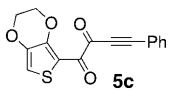
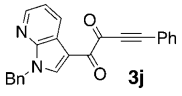
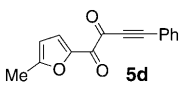
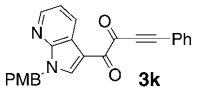
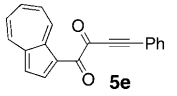
Table 1: Glyoxylation/Stephens–Castro synthesis of ynediones **3**, **4**, and **5**.[a]



Product	Yield [%][b] (method[c])	Product	Yield [%][b] (method[c])
 **3a**	66 (A)	 **4a**	64 (A)
 **3b**	68 (A)	 **4b**	74 (A)
 **3c**	73 (A)	 **4c**	67 (A)
 **3d**	60 (A)	 **4d**	60 (A)
 **3e**	43 (A)	 **4e**	77[d] (C)
 **3f**	74 (A)	 **4f**	44 (C)
 **3g**	57 (A)	 **5a**	47 (D)
 **3h**	35 (A)	 **5b**	53 (E)
 **3i**	2 (A)	 **5c**	66 (E)
 **3j**	62 (B)	 **5d**	38 (F)
 **3k**	59 (B)	 **5e**	33 (A)

[a] Reactions were performed in ethereal solvents [c(**1**) = 0.2 M] using 5.00 mmol of substrate **1**. Abbreviations: Ph = phenyl, Me = methyl, TIPS = triisopropylsilyl, Bu = butyl, Bn = benzyl, PMB = *p*-methoxybenzyl, Bzh = benzhydryl. [b] All yields refer to isolated and purified compounds. [c] Method A: THF, 0 °C to RT, 4 h; method B: DME, 0 °C to 100 °C, 2 h; method C: THF, 0 °C to 50 °C, 4 h; method D: DME, 0 °C to 100 °C, 24 h; method E: 1,4-dioxane, RT to 100 °C, 4 h; method F: 1,4-dioxane, RT to 100 °C, 24 h. [d] According to method A, 33 % of **4e** could be obtained.

active metal. Neither chelating ligands nor phosphanes are required.

The structures of the obtained ynediones **3**, **4**, and **5** were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis, and later by an X-ray structure analysis of compound **3a** (Figure 1).

The sequence proceeds smoothly in ethereal solvents (THF, DME, or 1,4-dioxane), thus making it possible to perform the glyoxylation step in a wide temperature range. The reaction with electron-rich indoles and 7-azaindoles gives derivatives functionalized in the 3-position exclusively (compounds **3a**–**k**). Generally, pyrroles give 2-substituted regioisomers without noticeable amounts of the 3-substituted isomers (compounds **4a**–**e**). Expectedly, when the substrate has a bulky substituent on the nitrogen atom of the pyrrole ring, the 3-position is functionalized (compound **4f**). To our great delight, other important heterocycles like pyrazole (compound **5a**), thiophene (compounds **5b** and **5c**), and furan (compound **5d**) could be converted to ynediones, although the glyoxylation of these heterocycles to glyoxylyl chlorides has never been described. Interestingly, there is a method describing a direct carboxylation of 1,3,5-trisubstituted pyrazoles with oxalyl chloride.[15] However, with 1-methyl-1*H*-pyrazole we observed no decarbonylation but instead formation of compound **5a**. A further advantage of the described Lewis acid free method is the possibility of reacting substrates that are not compatible with Lewis-acid-mediated Friedel–Crafts conditions and (compound **5d**). Surprising, however, was the observation that thiophenes turned out to be excellent substrates for the described sequence. The more electron-rich 2-methylfuran gave a lower yield of ynedione **5d** along with a by-product resulting from the condensation of two furan molecules with one molecule of oxalyl chloride in 14 % yield.

Furthermore, the electron-rich hydrocarbon azulene could be functionalized as well (compound **5e**).[16] Aryl acetylenes bearing electron-neutral (compounds **3a**, **3g**,**h**, **3j**,**k**, **4a**–**f**, and **5a**–**e**), electron-donating (compound **3b**), or electron-withdrawing (compounds **3c**,**d**) substituents can be carried through the sequence without difficulties. Also heteroaryl (compound **3e**) as well as TIPS-substituted acetylenes (compound **3f**) can be coupled efficiently. However, an alkyl acetylene gave a very poor yield (compound **3i**). In all cases, no decarbonylative products were observed. The products were easily isolated by flash chromatography and were usually obtained in analytically pure form as stable compounds.

The reactivity of the glyoxylation of π nucleophiles can be estimated by considering the nucleophilicity parameters N of the (hetero)aryl substrate as determined by Mayr et al. for some reference nucleophiles.[17] The nucleophilicity parameters of the employed (hetero)arenes range from approximately 1.26 to 6.66, spanning five orders of magnitude (see Table S8 in the Supporting Information).

Azoles, furans, and thiophenes are of paramount importance in the synthesis of products relevant for medicinal chemistry and material science as well as in the synthesis of natural products. Therefore, the described mild and easy-to-perform one-pot functionalization of these prevalent classes of heterocycles opens up remarkable possibilities for their

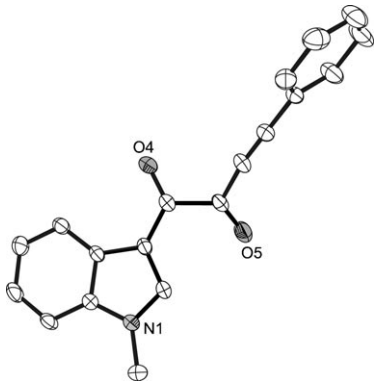
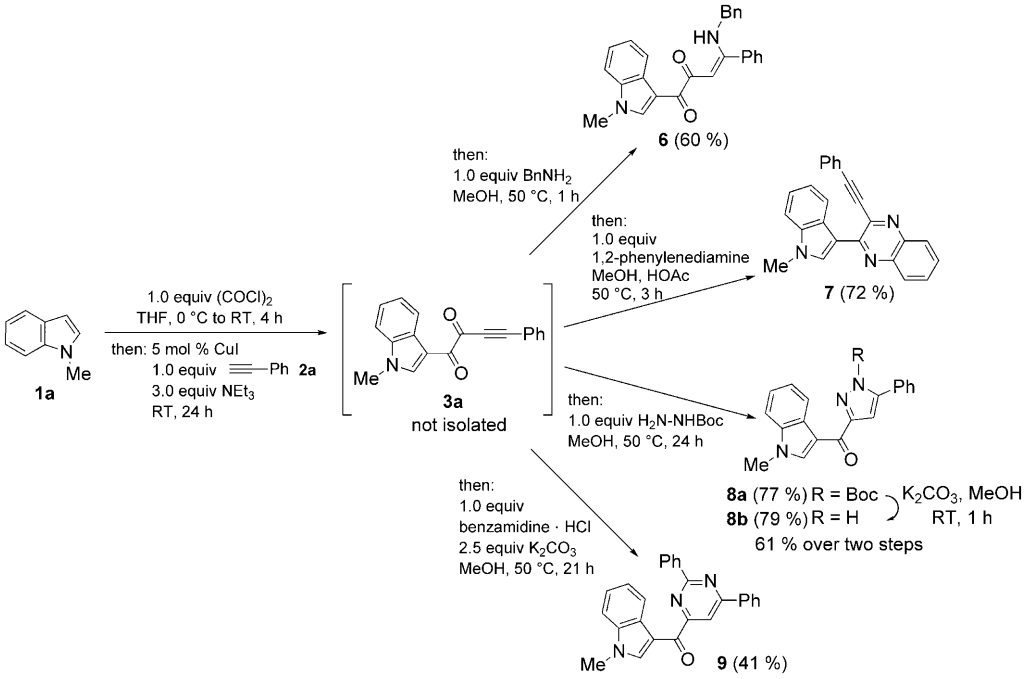


Figure 1. Molecular structure of **3a** (ellipsoids at the 50% probability level; hydrogen atoms were omitted for clarity).[18]

derivatization. Moreover, the obtained ynediones are densely functionalized, possessing a strongly activated Michael system as well as a dione motif, both important structural units in heterocycle synthesis.

As an illustration of the versatility of alkynediones as building blocks, we extended the sequence to the four-component syntheses of various products (Scheme 4). Simply by adding 1.0 equiv of different mono- and dinucleophiles after the glyoxylation/Stephens–Castro coupling sequence furnishing ynedione **3a**, we could achieve the one-pot syntheses of enaminedione **6**, quinoxaline **7**, indoloyl pyrazole **8a**, and indoloyl pyrimidine **9**; the final step of this sequence consists of Michael addition, double carbonyl condensation, and Michael addition/cyclocondensation reactions, respectively.



Scheme 4. Four-component syntheses of enaminedione **6**, quinoxaline **7**, indoloyl pyrazole **8a**, and indoloyl pyrimidine **9**.

It is worth mentioning that *tert*-butoxycarbonyl(Boc)-protected hydrazine can be used for the selective synthesis of the 2-acyl pyrazole **8a** without formation of the corresponding pyridazinone, thus giving direct and very efficient access to 2-acyl pyrazoles. So far, there has been no preparatively useful approach to this class of compounds. This unprecedented strategy is currently under investigation.

In conclusion, we have developed a new three-component approach to heterocyclic ynediones, which are very likely to become important intermediates in the synthesis of diverse, pharmaceutically interesting heterocycles. The use of catalytic Stephens–Castro conditions is crucial for the success of the reaction. The design of new diverse four-component syntheses of heterocycles with the intermediacy of ynediones has been highlighted successfully. It should be emphasized that all reagents in these three- and four-component reactions are required in equimolar ratios, rendering these sequences highly atom economical. Further generalizations of this strategy as well as diverse synthetic applications of ynediones are currently under investigation and will be reported in due course.

Experimental Section

3f: In an oven-dried screw-cap Schlenk flask with a septum a solution of 1-methyl indole (**1a**; 669 mg, 5.00 mmol) in 25 mL of anhydrous THF was placed under argon atmosphere. Argon was bubbled through the solution for 5 min which was cooled to 0 °C. Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), tris(isopropyl)silyl (**2f**; 1.13 mL, 5.00 mmol), and anhydrous triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture, and the reaction mixture was stirred at room temperature for 24 h. After complete conversion, distilled water (25 mL) was added, the phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, the residue was adsorbed onto Celite and purified by chromatography on silica gel (petroleum ether/ethyl acetate 7:1) to give the analytically pure **3f** (1.35 g; 74%) as a yellow solid, R_f = 0.25. M.p. 127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13–1.17 (m, 21H), 3.86 (s, 3H), 7.33–7.38 (m, 3H), 8.25 (s, 1H), 8.42–8.46 ppm (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.1 (CH), 18.5 (CH_3), 33.8 (CH_3), 103.4 ($C_{quat.}$), 103.9 ($C_{quat.}$), 109.9 (CH), 110.9 ($C_{quat.}$), 122.8 (CH), 123.5

(CH), 124.2 (CH), 127.2 ($C_{quat.}$), 137.3 ($C_{quat.}$), 140.0 (CH), 178.2 ($C_{quat.}$), 180.1 ppm ($C_{quat.}$). EIMS (70 eV) *m*/*z* (%): 367 $[M]^+$ (3), 158 $[M-C_{12}H_{21}OSi]^+$ (100), 130 $[C_9H_8N]^+$ (2). C,H,N analysis calcd (%) for $C_{22}H_{29}NO_2Si$ (367.6): C 71.89, H 7.95, N 3.81; found: C 72.06, H 7.94, N 3.70.

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