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Direct Access to β-Oxodiazo Compounds by Copper(II)-Catalyzed Oxidative Rearrangement of Stabilized Vinyl Diazo Derivatives

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S *Supporting Information*

ABSTRACT: The copper(II)-catalyzed reaction of alkenyldiazo compounds with iodosylbenzene leading to β-oxodiazo derivatives is reported. This process occurs via an unprecedented 1,2-shift of the diazoacetate function. A selection of the synthetic applications of a representative member of this new class of functionalized diazo derivatives in the regioselective synthesis of substituted 1,4-dicarbonyl compounds is also reported.

Past decades have witnessed the great impact of transition metal carbene intermediates in synthetic chemistry. While these metal species have been proposed as active intermediates in numerous catalytic cycles, direct precursors for their generation are rather scarce. In this regard, simple and unsaturated α-diazo carbonyl derivatives continue to be, after their discovery more than a century ago, the most valuable systems providing a vast array of transformations via their decomposition with transition metal catalysts.[1] In sharp contrast, routes to diazo compounds with remote functionalization are scarcely found.[2] In particular, *the β-oxodiazo system remains unknown.* An isolated contribution has been reported by Trost et al. who found that propargylic alcohols behave as β-oxocarbenoid precursors for the Ru-catalyzed intramolecular cyclopropanation reaction (Figure 1).[3]

Herein, we report that the treatment of vinyldiazocarbonyl compounds **1** with iodosylbenzene in the presence of a copper(II) catalyst represents a simple and general access to yet inaccessible γ-oxo-α-diazocarbonyl compounds **2** (Figure 2). This process comprises some significant features: (i) no oxidation of the diazo function of **1** and/or **2** occurs; (ii) unprecedented 1,2-migration of the C(EWG)=N_2 group takes place; (iii) as the alkenyldiazo compounds **1** are usually made by nucleophilic addition of lithium diazoacetate esters to carbonyls followed by dehydration,[4] the overall process can be seen as a formal two-step Cα−Cα′ coupling of a diazocarbonyl and a carbonyl.

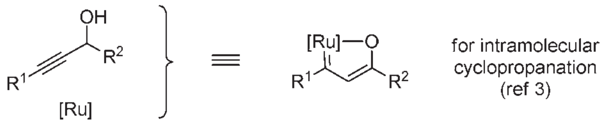

Figure 1. Propargyl alcohols as β-oxocarbene precursors.

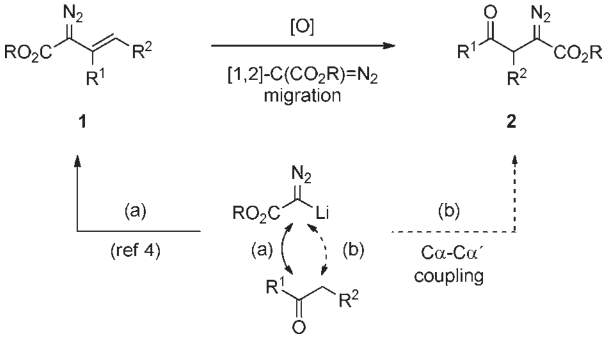

Figure 2. Formal Cα−Cα′ coupling approach to β-oxodiazo derivatives **2**.

According to our previous finding on the reactivity of vinyldiazoacetate esters through the vinyl moiety[5] we have selected iodosylbenzene as the electrophilic oxygen source. We found that stirring a mixture of compounds **1**, iodosylbenzene (1 equiv), and copper(II) triflate (5 mol %) in acetonitrile at room temperature led to the complete disappearance of the starting diazo compound after 5−10 min (TLC, 5:1 hexane/ethyl acetate). Purification by column chromatography (SiO_2, 5:1 hexane/ethyl acetate) afforded 4-oxodiazoacetates **2** in moderate to high isolated yield (43−92%) (Table 1).[6] In relation with the structure of the alkenyl moiety of the diazo substrate, some points are remarkable: (i) the process is more efficient for Cα-substituted (compound **1a**) than for unsubstituted or β-substituted diazo derivatives (compounds **1b**,**c**), whereas β-ethoxycarbonyl and β,β-disubstituted diazo compounds **1e**,**f** remain unaltered under the reaction conditions; (ii) carbocyclic and heterocyclic diazo compounds give the adducts **2g**−**i** in 50−66% yield. The oxidation of the diazophosphonate **1j** does not yield the expected oxodiazo derivative **2j**, but β-H elimination takes place instantaneously affording dimethyl (1*E*)-3-oxoprop-1-enylphosphonate **3j** in 68% yield.

Interestingly, the ketal protected diazo derivatives became available in a straightforward manner by using the corresponding alcohol as the solvent (Table 2).[7] Thus, stirring a mixture of ethyl 2-diazo-3-methylbut-3-enoate **1a** (R^1 = Me; EWG = COOEt), iodosylbenzene (1 equiv), and copper(II) triflate (5 mol %) in methanol (or methanol-D_4) afforded ethyl 2-diazo-4,4-dimethoxypentanoate **4a** in 98% isolated yield (**4a**-D_6; 95%). In a similar manner, ethyl, isopropyl, and allyl ketals **4b**,**c**,**d** are also formed in satisfactory yields. On the other hand, ethyl 2-diazobut-3-enoates **1b**/**1b**-D_1 (R^1 = H/D; EWG = COOEt) and ethyl 2-diazo-3-phenylbut-3-enoate **1k** (R^1 = Ph; EWG = COOEt) afforded the methyl ketals **4e**/**4e**-D_1 and **4f** in acceptable yields.

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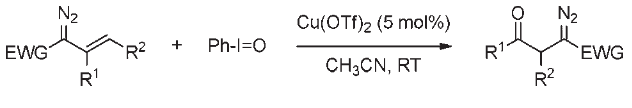
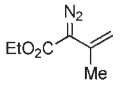
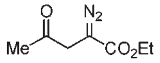
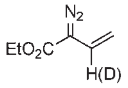
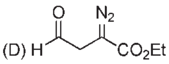
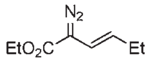
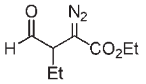
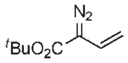
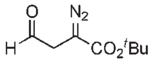
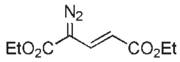
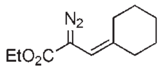
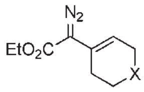
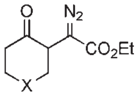
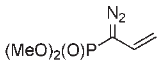
Table 1. Copper(II)-Catalyzed Synthesis of β-Oxodiazo-compounds 2 from Vinyldiazoacetates 1 and Iodosylbenzene

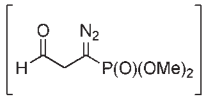


1 **2**

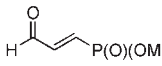
Substrate **1**		Product **2**		Yield[a]
	1a		2a	92%
	1b-H 1b-D$_1$		2b-H 2b-D$_1$	85% 75%
	1c		2c	58%
	1d		2d	43%
	1e	N/R		–
	1f	N/R		–
	1g (X = CH$_2$) 1h (X = O) 1i (X = N-BOC)		2g 2h 2i	66% 52% 50%



1j



2j



3j (68%)

[a] The reported yields are those of the products isolated after column chromatography.

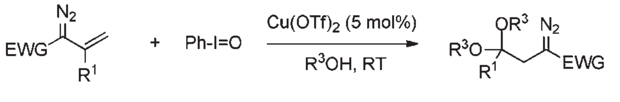
Diazo derivatives with other stabilizing groups, like acetyl and phosphonate, furnished compounds **4g,h** in 64−66% yield, thus providing a greater versatility for this transformation.[8]

A mechanistic proposal for the formation of diazo compounds **2** from vinyl diazoacetates **1** is outlined in Scheme 1. Initial nucleophilic attack of the C-β of **1** to the electrophilic species **I**, formed by coordination of iodosylbenzene and Cu(II),[9] would form the intermediate **II** which would cyclize to the oxonium species **III**. Then, reductive elimination of PhI and Cu(II) accompanied by the selective pinacol-like migration of the C(EWG)═N$_2$ moiety would complete the formation of diazo compounds **2**.

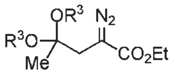
A similar mechanism would account for the alcoholysis of **1** leading to ketal derivatives **4**. In this case, the participation of intermediates **I′**−**IV′** are thought to be involved in the process.[10] Based on the observed influence of substituents R^1, R^2, the formation of **II** (**II′**) is proposed to be the rate-determining step.[11]

Preliminary studies on the potential application of these functionalized diazo compounds were undertaken using compound **2a** as the model substrate. It must be noted that compounds **2** would give access to 1,4-dicarbonyl compounds with substitution/functionalization at a predefined α-position.[12] In Scheme 2 some C−C and C−O bond-forming reactions of the diazo functionality are illustrated. First, the [Cu(MeCN)$_4$][BF$_4$]-catalyzed β-H elimination of **2a** afforded the alkene **3a** with complete *E*-stereoselectivity (see also compound **3j** in Table 1).[13,14] The cyclopropanation reaction toward styrene and butylvinyl ether was accomplished with the simplest rhodium(II) catalyst, Rh$_2$(OAc)$_4$, to provide functionalized cyclopropanes **5a,b** in moderate yields and complete *trans*-stereoselectivity.[15] On the other hand, the Rh$_2$(OAc)$_4$-catalyzed O−H insertion reaction of

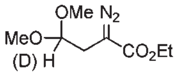
Table 2. Copper(II)-Catalyzed Synthesis of β,β-Dialkoxy-diazo Compounds 4 from Vinyldiazo Compounds 1 and Iodosylbenzene[a]



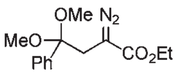
1 **4**



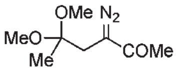
4a (R^3 = Me), 98%
4a-D$_6$ (R^3 = CD$_3$), 95%
4b (R^3 = Et), 72%
4c (R^3 = iPr), 55%
4d (R^3 = allyl), 61%



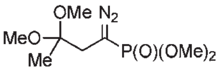
4e, 55%
4e-D$_1$, 62%



4f, 60%



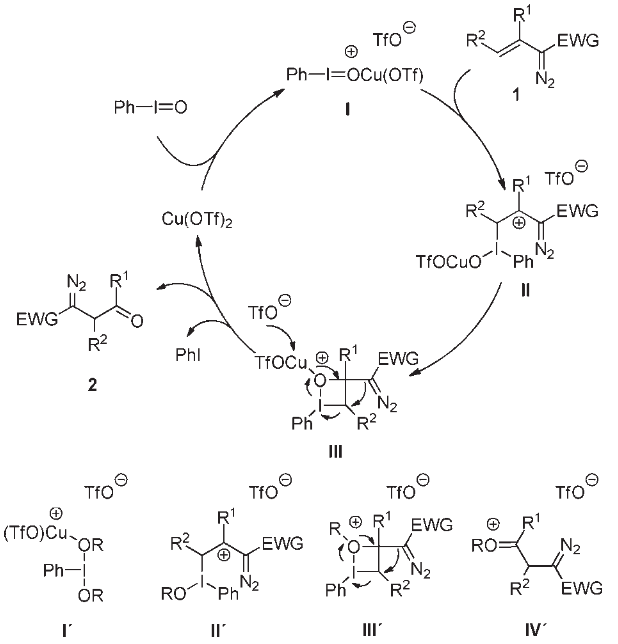
4g, 64%



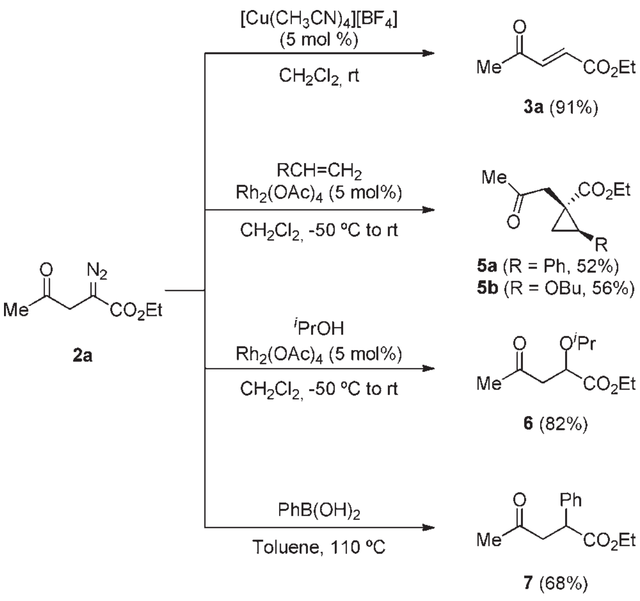
4h, 66%

[a] Yields of the isolated products after column chromatography.

Scheme 1. Mechanistic Hypothesis for the Formation of Diazo Compounds 2 and 4 from Vinyldiazo Compounds 1 and Iodosylbenzene



Scheme 2. Representative Synthetic Applications of Diazo Compound 2a[a]



[a] The reported yields are those of the isolated products after purification by column chromatography.

isopropanol led efficiently to the γ-oxo-α-isopropoxypentanoate ester **6**.[16] Interestingly, the metal-free arylation allowed the selective creation of a C−C bond at the diazo function giving rise to **7** in a synthetically useful yield.[17]

In summary, we have developed a convenient Cu(II)-catalyzed synthesis of novel β-oxodiazo compounds and their ketal-protected derivatives from vinyldiazo compounds and iodosylbenzene via an unprecedented oxidation/1,2-shift of the diazoacetate function. The easy access to this new building block featuring two significant β-functionalities (carbonyl and diazo groups) will likely be useful in designing new synthetic methodologies. Thus, fundamental diazo transformations (β-H elimination, cyclopropanation, O−H insertion, reductive arylation) work well allowing for the regioselective preparation of an array of 1,4-dicarbonyl derivatives with hetero- and carbosubstitution at a specific α-position.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Full experimental details and spectral data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) For a recent review on the synthesis of diazo compounds, see: (a) Maas, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 8186. For selected reports on remote functionalized diazo compounds, see: (b) Xu, X.; Hu, W.-H.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 6392. (c) Zhou, L.; Doyle, M. P. *Org. Lett.* **2010**, *12*, 796. (d) Yu, L.; Zhang, Y.; Jee, N.; Doyle, M. P. *Org. Lett.* **2008**, *10*, 1605. (e) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171. (f) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2773. (g) Liao, M.; Dong, S.; Deng, G.; Wang, J. *Tetrahedron Lett.* **2006**, *47*, 4537. (h) Zhao, Y.; Wang, J. *Synlett* **2005**, 28886. (i) Dong, C.; Mo, F.; Wang, J. *J. Org. Chem.* **2008**, *73*, 1971. (j) Dong, C.; Deng, G.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5560. (k) Padwa, A.; Zhang, Z. J.; Zhi, L. *J. Org. Chem.* **2000**, *65*, 5223.

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(5) Barluenga, J.; Riesgo, L.; López, L. A.; Rubio, E.; Tomás, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7569.

(6) Control experiments demonstrated that no reaction takes place in the absence of the copper catalyst. Screening of other catalysts led to much poorer results. In particular, various copper(I) catalysts afforded complex mixtures of products.

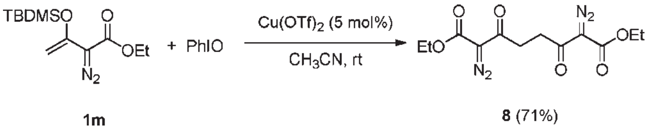
(7) The use of alcohols as the solvent in reactions involving iodosylbenzene is a common practice. The high solubility of this reagent in these solvents is ascribed to its solvolysis that forms iodobenzene dialkoxide, PhI(OR)$_2$. See: Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, *22*, 1563.

(8) Diazomethylphosphonate esters are precursors of cyclopropylphosphonates, a class of compounds with potential biological activity: Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 2117.

(9) The exact nature of the intermediates involved in the reaction of iodosylbenzene and copper(II) ions is unclear. See, for example: Franklin, C. C.; VanAtta, R. B.; Tai, A. F.; Valentine, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 814.

(10) A control experiment (**2a**, Cu(OTf)$_2$, 5 mol%, MeOH, rt, 2 h) confirmed that ketals **4** are not formed from the corresponding ketones **2**.

(11) When a more nucleophilic substrate, like the silyloxy-substituted vinyl diazoacetate **1m** (R^1 = OSiMe$_2$*t*Bu), was employed the reaction followed a different pathway affording the expected dimerization product **8**. For the dimerization of simple silylenol ethers, see: Zhdankin, V. V.; Mullikin, M.; Tykwinski, R.; Berglund, B.; Caple, R.; Zefirov, N. S.; Koz'min, A. S. *J. Org. Chem.* **1989**, *54*, 2605.



(12) This methodology would be a practical experimental protocol for the indirect, chemoselective substitution reactions of unsymmetrical 1,4-dicarbonyl systems. For selected recent regioselective syntheses of substituted γ-keto esters, see: (a) Gururaja, G. N.; Mobin, S. M.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2011**, 2048. (b) Wang, W.; Xu, B.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 1640. (c) Zhao, W.-J.; Yan, M.; Huang, D.; Ji, S.-J. *Tetrahedron* **2005**, *61*, 5585.

(13) We have experienced that thermal induced elimination (toluene, 110 °C) produces the *Z*-alkene as the major stereoisomer (*Z*/*E* = 4:1). For the *Z*-selective Rh(II)-catalyzed elimination in alkyldiazoacetates, see: Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia,

J. M. *J. Org. Chem.* **1996**, *61*, 2908. In our case, Rh(II)-catalyzed elimination from **2a** led to the *Z*-alkene in a very low yield.

(14) For access to this type of alkenes by cross-coupling of diazo compounds, see: Hansen, J. H.; Parr, B. T.; Pelphrey, P.; Jin, Q.; Autschbach, J.; Davies, H. M. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 2544.

(15) The Rh(II)-catalyzed diastereoselective cyclopropanation of alkenes with α-alkyl-α-diazoesters has been recently reported: Panne, P.; DeAngelis, A.; Fox, J. M. *Org. Lett.* **2008**, *10*, 2987.

(16) For a review on the synthetic applications of the O−H insertion reactions of carbenes and carbenoides derived from diazocarbonyl and related diazo compounds, see: Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811. See also ref 1.

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