Dipolar Cycloaddition Reactions

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Copper-Promoted Cycloaddition of Diazocarbonyl Compounds and Acetylides**

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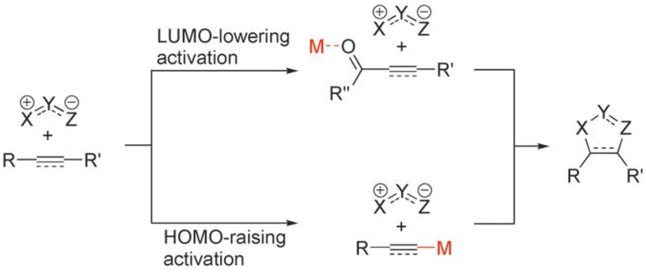
1,3-Dipolar cycloaddition reactions provide convenient access to carbocyclic and heterocyclic five-membered ring systems.[1] In some cases, 1,3-dipoles react with dipolarophiles without activation of either component. For example, the ozonolysis of olefins and the addition of nitrile oxides to alkynes often proceed without added promoters.[2] With many substrate combinations, however, no cycloadduct is formed when the dipole and dipolarophile are simply mixed. To accelerate these types of reactions, two complementary strategies focus on modulating the reactivity of the dipolarophile (Scheme 1). In the first, Lewis acids are included to lower the energy of the LUMO of the dipolarophile.[3] Under such conditions the dipole reacts through its HOMO to generate the cycloaddition product.[4] Alternatively, additives that increase the electron density of the dipolarophile can accelerate cycloaddition through a HOMO$_{(dipolarophile)}$–LUMO$_{(dipole)}$ interaction. This approach is less common than the methods based on Lewis acids,[5] but is most notably operative in the copper-catalyzed synthesis of triazoles from alkynes and azides.[6] Here we report a new example of dipolar cycloaddition reactions with an inverse electron demand: the synthesis of pyrazoles from the cycloaddition of copper acetylides with diazocarbonyl compounds [Eq. (1)].



Scheme 1. Activation of alkynes and alkenes by metals for 1,3-dipolar cycloaddition reactions. LUMO = lowest unoccupied molecular orbital, HOMO = highest occupied molecular orbital, M = metal.

The pyrazole substructure appears in small molecules which possess a wide range of biological activities, and accordingly represents a valuable target for organic synthesis.[7] A common tactic for the preparation of pyrazoles **1** relies on the condensation of β-diketones with hydrazines.[8] Alternatively, the cyclization reaction of diazoalkenes[9] or unsaturated hydrazines[10] provides improved control of regiochemistry relative to the dicarbonyl/hydrazine condensation, although the precursors are more challenging to prepare. A direct approach to pyrazoles involves the cycloaddition of diazo compounds with alkynes. In this regard, electron-rich diazo compounds (such as diazomethane) react under mild conditions with electron-deficient alkynes.[11] In contrast, Lewis acids are required to promote the cycloaddition between electron-deficient alkynes and diazocarbonyl compounds.[12] However, simple alkyl or aryl acetylenes generally fail to react with diazocarbonyl compounds under thermal conditions or in the presence of Lewis acids. To identify an alternative mode of activation, we evaluated metal acetylides in cycloaddition reactions with diazocarbonyl compounds.

When lithium phenylacetylide was treated successively with various copper(I) sources and benzyl diazoacetate (**2**), pyrazole **1a** was formed along with benzyl alcohol (BnOH, Table 1). In all cases, the conversion of the diazoester reached completion, and, with one exception, more than 90% of the mass balance was accounted for by **1a**, BnOH, and recovered alkyne. Fumarate and maleate side products were observed in less than 5% yield, which allowed the use of equimolar quantities of reagents. An alkali-metal acetylide was required, and in the absence of copper, no pyrazole was formed. Systematic variation of the copper source, base, and additive led to the discovery that $CuCN \cdot 6LiCl$[13] minimized the formation of BnOH and maximized the yield of the pyrazole **1a** (entry 8, Table 1).[14] The relationship between the components of the reaction mixture and the product distribution was found to be complex. For example, while the inclusion of LiCl did not improve the reactions which involved CuI (entry 1 versus 3, Table 1), small but reproducible enhancements in the **1a**/BnOH ratio were observed when up to six equivalents of LiCl were added to the reaction mixtures that contained CuCN (entries 5–9, Table 1). Similarly, whereas complex mixtures were produced from 1:1 molar ratios of CuI and alkyne, optimal results were obtained when the lower-order cuprate derived from $CuCN \cdot 6LiCl$ was used (entry 1 versus 2, and 4 versus 5; Table 1).

The cycloaddition reaction displayed substantial generality with respect to both the alkyne and diazocarbonyl component, and in all cases the product was formed as a single regioisomer (Scheme 2). Electron-poor and electron-

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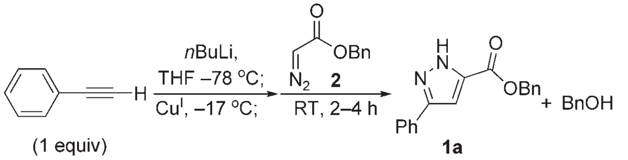
Table 1: Influence of copper source and LiCl on the cycloaddition reaction of lithium phenylacetylide with benzyl diazoacetate.[a]



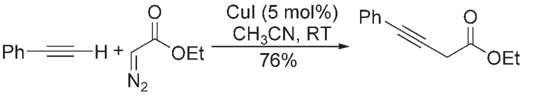
(1)

Entry	Cu^{I}	Equiv Cu^{I}	Ratio **1a**/BnOH[b]
1	CuI	0.5	1.5:1
2	CuI	1.0	–[c]
3	CuI·2 LiCl	0.5	0.9:1
4	CuCN	0.5	2.0:1
5	CuCN	1.0	4.0:1
6	CuCN·2 LiCl	1.0	5.4:1
7	CuCN·4 LiCl	1.0	5.9:1
8	**CuCN·6 LiCl**	**1.0**	**6.0:1**
9	CuCN·8 LiCl	1.0	5.4:1

[a] Complete conversion of diazoester was observed in all cases. Mass balances were > 90% as determined by ^{1}H NMR spectroscopy relative to an internal standard (except entry 2). [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Complex mixture.

rich aryl acetylenes performed well in the cycloaddition. Alkyl-substituted terminal alkynes reacted cleanly, and halides, tertiary amino groups, esters, and nitriles were tolerated. The reaction was not limited to benzyl diazoacetate as the ethyl and *tert*-butyl diazoesters and Weinreb amides performed similarly in the cycloaddition. In many cases, the pyrazoles could be isolated in greater than 90% purity by trituration with hexanes; in all cases, analytically pure product could be isolated after column chromatography on silica gel.

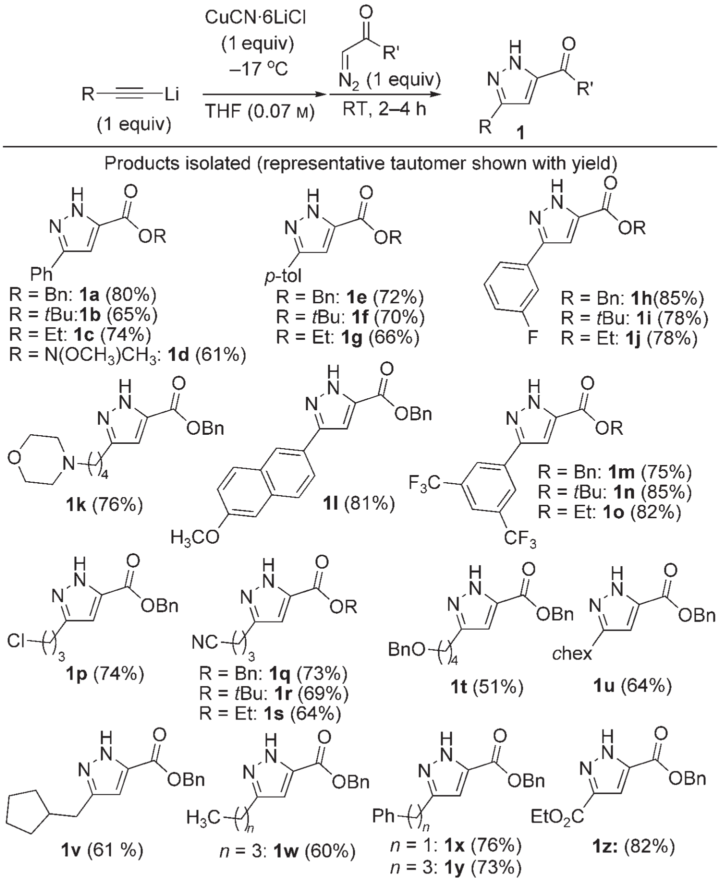
Comparisons between the present cycloaddition reaction and two known reactions are striking. First, Suárez and Fu described a Cu^{I}-catalyzed alkynylation of diazoesters [Eq. (2)][15] in which no pyrazole was formed under the



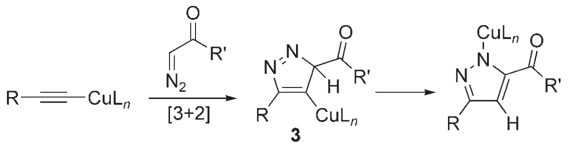
(2)

neutral conditions. Likewise, the reaction of ethyl dizaoacetate with PhCCLi/CuCN·6LiCl gave no observable alkynyl ester. The critical difference between the two systems is likely the protonation state of the alkyne; alkynyl anions were used in the cycloaddition reaction whereas neutral alkynes were involved in the reaction reported by Suárez and Fu. The amount of copper used in the reaction does not appear to have been significant, as even catalytic amounts of CuI was found to promote the cycloaddition of lithium phenylacetylene and benzyl diazoacetate.

The copper-mediated cycloaddition of alkynyl anions with diazoesters is also reminiscent of the copper-catalyzed cycloaddition of terminal alkynes with azides.[16] Accordingly, we suspect a similar reaction mechanism is operative in both cases. Copper may serve as an electron-donating group and raise the energy of the HOMO of the alkyne. A cycloaddition that involves the LUMO of the diazocarbonyl compound generates a (pyrazolyl)Cu intermediate **3** which can tautomerize under the reaction conditions (Scheme 3). This proposal accounts for several important observations: First, the fact that the reaction rate is similar in THF, ether, and

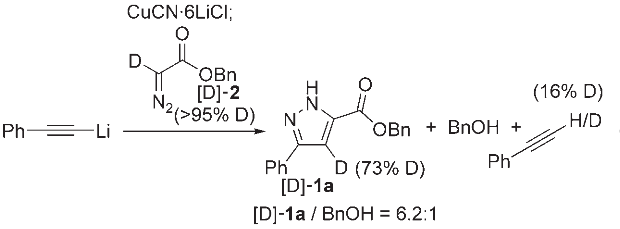


Scheme 2. Copper-promoted reaction of lithium acetylides with diazo carbonyl compounds. *c*hex = cyclohexyl, *p*-tol = para-tolyl.



Scheme 3. Proposed cycloaddition reaction of copper acetylide with diazo carbonyl compounds. L = ligand.

toluene is consistent with a concerted cycloaddition process but is not consistent with the stepwise formation of charged intermediates. Second, the observed regioselectivity is consistent with theoretical predictions for cycloadditions featuring HOMO$_{(\mathrm{dipolarophile})}$–LUMO$_{(\mathrm{dipole})}$ interactions.[4] Third, electron-withdrawing groups on the alkyne qualitatively slow the reaction. These groups should lower the energy of the HOMO of the alkyne and therefore increase the gap between the HOMO and LUMO energy levels. Fourth, diazomethane does not react with lithium acetylides under the reaction conditions, which is presumably a reflection of its high-energy LUMO relative to that of the diazoesters. Finally, deuterium-labeling experiments support the proposed tautomerization, in that the copper-mediated cycloaddition reaction with the α-deuterated benzyl diazoacetate [D]-**2** yielded [D]-**1a** with substantial deuterium incorporation on the pyrazole ring [Eq. (3)]. Additionally, recovered phenylacetylene was partially deuterated, which likely reflects deprotonation of the initial cycloadduct **3** by the alkynyl anion.[17]



(3)

The origin of the BnOH side product is not clear at present, although several mechanisms for its formation can be ruled out. The generation of BnOH requires use of a general base and not acetylides or copper salts specifically: benzyl diazoacetate reacted completely with butyllithium, $[Li_2Cu(n\text{-}C_4H_9)_2CN]$, lithium phenylacetylide, or lithium diisopropylamide (LDA) to yield BnOH as the major product under mild conditions. These results, and the fact that the pyrazole is stable under the reaction conditions, implicate benzyl diazoacetate as the source of BnOH. In principle, direct E_2 elimination of alkoxide from benzyl diazoacetate could account for the formation of BnOH. If so, a reduction in the kinetic acidity of **2a** might increase the ratio of **1a**/BnOH.[18] In practice, however, reactions with **2** or [D]-**2** gave nearly identical ratios of **1a**/BnOH [compare entry 8, Table 1 and Eq. (3)]. Additionally, since the recovered phenylacetylene was only partially deuterated, the deprotonation could not account for all of the BnOH formation. Direct addition to the carbonyl group could release BnOH, yet such a pathway is not supported by the results. In particular, phenylacetylene was recovered after the reaction, and no addition products are observed in the crude reaction mixtures. Furthermore, the similar yields of pyrazoles obtained with small (ethyl) and large (*tert*-butyl) diazoester groups does not support a competing mechanism that involves addition to the carbonyl group. Finally, simple ester hydrolysis appears unlikely. Specifically, the reactions performed with varying substoichiometric amounts of water yielded similar amounts of BnOH, while excess water was found to inhibit the reaction. Furthermore, the amount of BnOH produced was inversely related to the amount of LiCl (a possible source of water) that was included in the reaction mixture.

The copper-promoted cycloaddition reaction of acetylides with diazocarbonyl compounds offers a direct and efficient approach to the synthesis of pyrazoles. The method is operationally simple and tolerates substantial variation in the two reacting partners. Furthermore, as a rare example of an inverse-electron-demand cycloaddition, it represents a conceptually novel approach to this important class of heterocycles. Ongoing studies seek clarification of the mechanisms responsible for pyrazole and side-product formation with an aim to identify reaction parameters which favor the former over the latter.

Experimental Section

BuLi (1.0 mmol) was added to a solution of alkyne (1.0 mmol) in THF (4 mL) at −78 °C. After 1 h this solution was transferred into a solution of CuCN·6LiCl (1.0 mmol) in THF (6 mL). The reaction mixture was warmed to −17 °C (dry ice/brine) and stirred for 1 h. A solution of diazo compound (1.0 mmol) in THF (4 mL) was added. After stirring for 2–4 h at RT, aq NH_4Cl and diethyl ether were added. The aqueous layer was extracted with diethyl ether and the combined organic phases were concentrated and purified by flash chromatography. The data for full characterization of the products can be found in the Supporting Information.

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