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Novel Ag(I)-Catalysis of an Intramolecular 1,3-Dipolar Cycloaddition.

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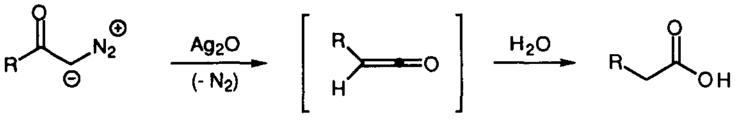
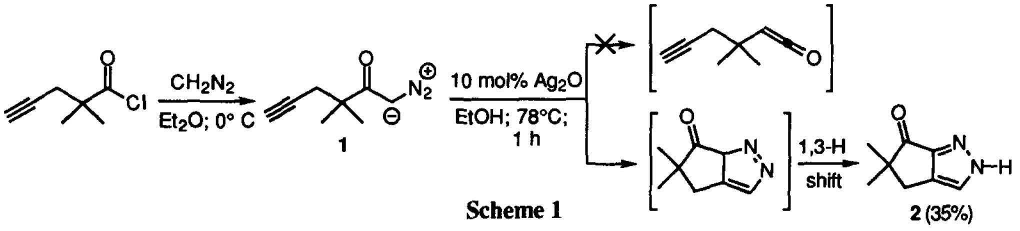
Abstract: *Acetylenic α-diazoketones, bearing gem-dimethyl substituents in the α′ position, were found to undergo an intramolecular 1,3-dipolar cycloaddition reaction in the presence of silver(I) as catalyst. In that instance, bicyclic pyrazole derivatives were isolated in 47 to 55% yield, even in the conditions of the Arndt-Eistert reaction. The requirement for gem-dimethyl substitution in acyclic substrates is rationalized in terms of steric effects on conformational energies in the transition state.*

The use of α-diazoketones as key intermediates in organic synthesis has seen revived recent interest.[1] However, perhaps the most important role of these compounds remains as starting materials for the Arndt-Eistert homologation of carboxylic acids.[2] This sequence proceeds by way of the Wolff rearrangement of an α-diazoketone to a ketene, a process usually carried out employing Ag_2O as a catalyst.[3]



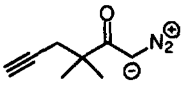
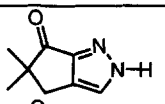
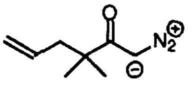
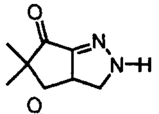
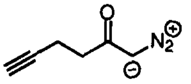
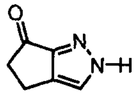
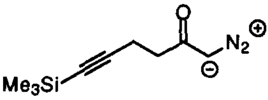
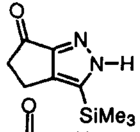
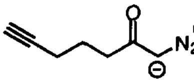
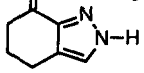
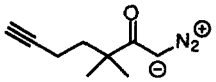
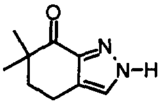
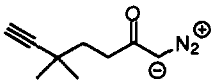
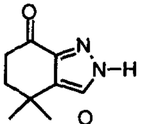
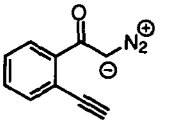
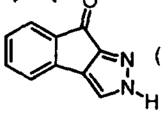
We now report a remarkable side reaction of certain alkynyl α-diazoketones catalyzed by silver(I), in which the normal Wolff rearrangement is circumvented. This side reaction comprises a metal-catalyzed intramolecular 1,3-dipolar cycloaddition and leads to novel polycyclic pyrazole derivatives. Whereas silver fluoride has been previously used to generate azomethine ylides that undergo 1,3-dipolar cycloaddition with several dipolarophiles,[4] we are unaware of precedent for silver(I)-catalysis of an otherwise unobserved 1,3-dipolar cycloaddition involving a preformed 1,3-dipole.

Our initial aim was to synthesize the homologous ester, ethyl 3,3-dimethyl-5-hexynoate, from the α-diazoketone **1**, prepared in the usual manner[5] from the acid chloride shown.[6] When α-diazoketone **1** was refluxed in dry ethanol in the presence of 10 mol% of Ag_2O for one hour, no trace of Wolff rearrangement product was observed. We isolated instead a 35% yield of a crystalline product, m.p. 120-122° C, having carbonyl absorption at 1705 cm^{-1}. The structure of this product was assigned as the pyrazole **2** (Scheme 1) on the basis of detailed analytical and spectroscopic data.[7] Control experiments omitting Ag_2O showed the α-diazoketone **1** to be stable for 24 h in refluxing ethanol. The formation of fused bicyclic pyrazole **2** was observed in several common solvents (EtOH, MeCN, aq. dioxane, THF) but the best result (47%; Entry 1) was obtained in refluxing THF for 3 h using 20 mol% of Ag_2CO_3/Celite as the catalyst.[7] The use of mercuric trifluoroacetate instead of Ag_2CO_3 gave a comparable result. When the terminal alkyne was replaced by an alkene, the diazoketone **3** did not react at all, giving complete recovery of starting material after 16 h in refluxing THF (Entry 2).



Scheme 1

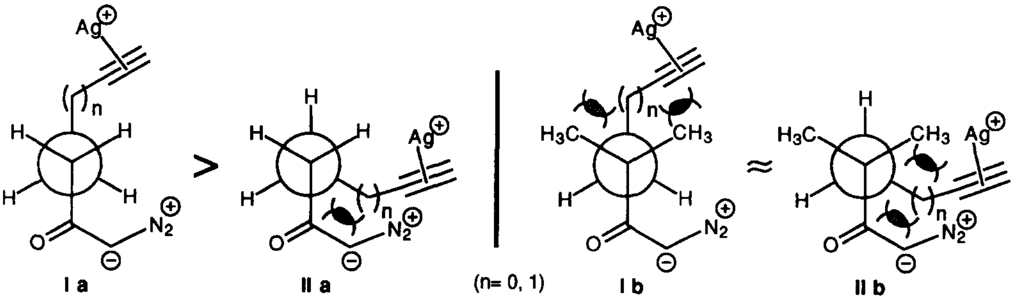
As shown in the Table, our catalyzed intramolecular 1,3-dipolar cycloaddition was highly sensitive to structure, in that for the aliphatic substrates (Entries 1-7) *gem*-dimethyl substituents α' to carbonyl were essential for the reaction to occur. Linear α-diazoketones lacking this feature gave no cycloadduct after several hours in refluxing THF with Ag_2CO_3/Celite. Compounds 5 and 9 did undergo the Wolff rearrangement in refluxing ethanol with 10 mol% Ag_2O, giving the homologous esters in high yield.

Entry	α-Diazoketone	Time (h)[a]	Predicted cycloadduct[b]	Yield (%)
1	 (1)	3	 (2)	47[c]
2	 (3)	16	 (4)	0[d]
3	 (5)	4	 (6)	0[d]
4	 (7)	20	 (8)	0[d]
5	 (9)	24	 (10)	0[d]
6	 (11)	3	 (12)	55[c]
7	 (13)	22	 (14)	0[d]
8	 (15)	3	 (16)	69[c]

a) All reactions were performed in refluxing THF using 20 mol% of Ag_2CO_3/Celite as catalyst; b) position of the pyrazole NH is arbitrarily assigned since we can not differentiate reliably between NH tautomers; c) isolated yield; d) recovered starting material when THF was solvent.

We postulate that the novel catalyzed cyclizations involve the activation of the acetylenic bond by coordination with Ag(I), an apparently new observation for 1,3-cycloadditions. It is less clear why the presence of *gem*-dimethyl groups α' to carbonyl (but not γ' to carbonyl) favor the catalyzed cyclization. Since the substrate **13** gave no cycloadduct (Entry 7), a simple Thorpe-Ingold effect[8] of the *gem*-dimethyl group does not appear to rationalize these data. It is clear that any entropic factors which favor the proximity of the two reacting functional groups would accelerate the cyclization. This is supported by the efficient cyclization of the aromatic model **15** to the tricyclic pyrazole **16** in 69% yield (Entry 8).

A possible rationalization of the α'-*gem*-dimethyl effect may involve the effect of these substituents on the activation energies for cyclization. Thus, the most stable rotamer **Ia** has the two reacting functional groups in the antiperiplanar position. Rotamer **IIa**, which would allow the cyclization, develops a non-bonding interaction between both functionalities with an increment of the A-value of the triple bond due to its complexation with silver(I). The difference of energy between rotamer **Ib** *versus* **IIb** is less for α-diazoketones bearing a *gem*-dimethyl group in the α' position. This is due to a non-bonding interaction between the acetylenic function and the methyl substituents which is present in the unreactive rotamer **Ib** (Scheme 2). This may account for the fact that the cyclization of **11** also yielded (55%; Entry 6) the 6,5-membered bicyclic pyrazole compound **12**.[9]



Scheme 2

Thus, we have shown the first examples of metal ion catalysis of a 1,3-dipolar cycloaddition, whereby structurally novel fused pyrazoles are formed. These observations raise the question whether electrophile-catalysis at 1,3-dipolar cycloadditions may have broader generality.[10]

References and notes:

(1) For a review, see: Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385-5453.

(2) Regitz, M.; Mass, G. in "*Diazo Compounds: Properties and Synthesis*"; Academic Press, Orlando, Fl. 1986, p 185.

(3) a) Bachmann, W. E.; Struve, W. S. *Org. Reactions* **1941**, *1*, 38-62; b) It is noteworthy that the Wolff rearrangement can be also performed under photochemical conditions: Horner, A. L.; Spietschka, E.; Gross, A. *Ann.* **1951**, *573*, 17-30.

(4) Padwa, A.; Dent, W.; Nimmesgern, H.; Venkatramaman, M. K.; Wong, G. S. K. *Chem. Ber.* **1986**, *119*, 813-828.

(5) Arndt, F.; Eistert, B., Amende, J. *Ber.* **1928**, *61*, 1949-1953.

(6) 2,2-dimethyl-4-pentynoyl chloride was prepared by the following 3 steps in 80% yield: i) alkylation of the lithium derivative of methyl *iso*butyrate by propargyl bromide (96%); ii) saponification with KOH in refluxing ethanol (89%); iii) reaction with $(COCl)_2$ in benzene using a catalytic amount of DMF (94%).

(7) **Typical procedure:** To a solution of the α-diazoketone (1 mmol) in 10 mL of THF, was added at r.t. Ag_2CO_3/Celite (1/1; 110 mg, 0.2 mmol) in one portion. The mixture was then allowed to reflux and the reaction was monitored by TLC. After having been cooled at r.t., the solution was filtered in vacuo and concentrated. The residue was purified by column chromatography (silica) using an 80/20 mixture of ethyl ether and hexanes as eluent.

2: 47%; R_f= 0.30 (80 Et_2O/20 Hex); m.p: 120-122° C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1 H), 2.81 (s, 2 H), 1.32 (s, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 201.0, 149.0, 139.2, 130.8, 53.9, 35.5, 26.2; IR ($CHCl_3$) 3300, 2960, 1705, 1385, 1305, 1000, 965, 915 cm^{-1}; Anal. calcd. for $C_8H_{10}ON_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.85; H, 6.94; N, 18.52.

12: 55%; R_f= 0.30 (80 Et_2O/20 Hex); m.p: 188-190° C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 2.81 (t, J= 6.1 Hz, 2 H), 2.01 (t, J= 6.1 Hz, 2 H), 1.25 (s, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 196.9, 140.0, 132.5, 125.9, 43.1, 38.7, 23.7, 17.3; IR ($CHCl_3$) 3450, 2960, 1675, 1385, 1290, 930, 900, 850 cm^{-1}; Anal. calcd. for $C_9H_{12}ON_2$: C, 65.83; H, 7.36; N, 17.06. Found: C, 65.80; H, 7.39; N, 16.79.

16: 69%; R_f= 0.25 (100% Et_2O); m.p: 212-214° C; ^{1}H-NMR (300 MHz, CD_3OD) δ 7.59 (s, 1 H), 7.47 (d, J= 7.3 Hz, 1 H), 7.42 (t, J= 7.3 Hz, 1 H), 7.27 (d, J= 7.3 Hz, 1 H), 7.17 (t, J= 7.3 Hz, 1 H); ^{13}C-NMR (75 MHz, CD_3OD) δ 187.7, 139.5, 139.1, 136.2, 135.8, 128.5, 125.4, 123.1, 122.5, 121.8; IR (Nujol) 3150, 3060, 1715, 1610, 1290, 1190, 1150, 1060, 1030, 895, 760, 730 cm^{-1}; Anal. calcd. for $C_{10}H_6ON_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.56; H, 3.64; N, 16.27.

(8) a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080-1106; b) Ingold, C. K. *Ibid.* **1921**, *119*, 305-329.

(9) The ^{1}H-NMR spectra of compounds **1** and **11** (which undergo the intramolecular cycloaddition) differ from those of **5**, **9** and **13** in that the α-CH of the first pair appears as a sharp singlet at room temperature, whereas the corresponding α-CH in the latter three appears as a broad signal which for **13** coalesces to a sharp singlet above 50° C. This could suggest a conformational preference for **IIb** in the former pair, but multiple rotamer populations in the latter three, consistent with our rationale.

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