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REGIOSELECTIVE SYNTHESIS OF DIHYDROFURANS FROM 2,2-DIBROMO-1,3-DIKETONE AND OLEFIN USING COPPER

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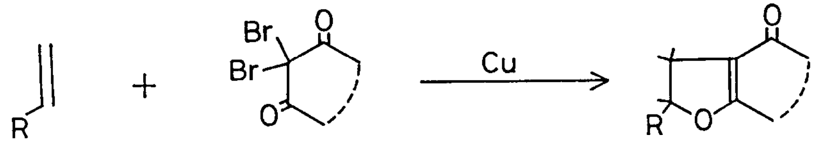
SUMMARY: 2,2-Dibromo-1,3-diketones reacted with copper powder and olefin to give 4,5-dihydrofuran derivatives in a highly regioselective fashion.

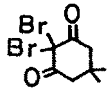
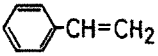
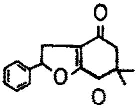
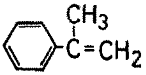
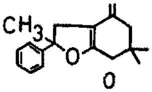
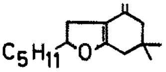
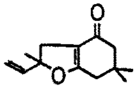
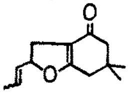
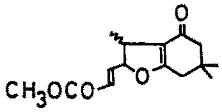
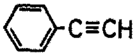
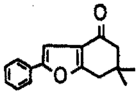
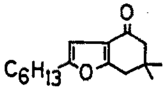
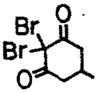
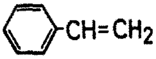
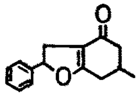
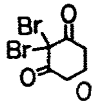
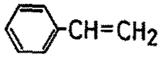
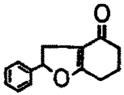
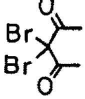
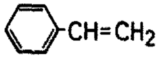
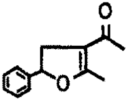
In light of the chemistry of keto-carbenoids as 1,3-dipoles,[1,2] we have been interested in reduction of gem-dibromides having adjacent carbonyl functionality with low valent metals.[2] Herein we wish to report that the reduction of 2,2-dibromo-1,3-diketones with copper powder in the presence of olefins afforded 4,5-dihydrofurans, formal 1,3-dipolar cycloadducts.



In a typical procedure copper powder (393 mg, 6.18 mmol) was activated by stirring with iodine (13 mg, 0.10 mmol) in 2.0 ml of benzene at room temperature until the color of iodine disappeared. 2,2-Dibromo-5,5-dimethyl-1,3-cyclohexanedione (886 mg, 2.97 mmol) and styrene (202 mg, 1.94 mmol) were added and the mixture was allowed to react at 75 °C for 2 h. Filtration and chromatography on silica gel afforded 412 mg (88% yield) of 2-phenyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran. The reaction was also carried out in dimethyl sulfoxide (DMSO) at room temperature. In this case activation of copper by iodine was not neccessary.

Various olefins reacted with 2,2-dibromo-1,3-diketones and copper in a similar fashion to give the corresponding dihydrofuran derivatives (Table I). Extremely high regioselectivity should be noted. Oxygen atom of dibromodiketone added selectively onto the more substituted carbon of the terminal olefin. The other regioisomer was not detected. Conjugated dienes reacted in a 1,2-fashion to give single regioisomers. Acetylenes also afforded cycloadducts, furan derivatives under similar conditions.

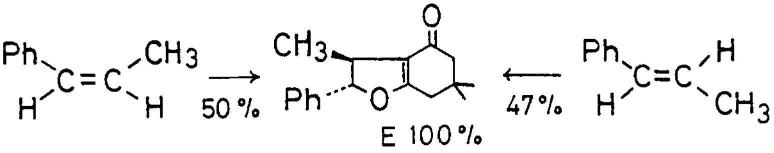
Table I Synthesis of Dihydrofurans[a]

dibromodiketone	olefin or acetylene	solvent	time h	product	yield %[b]
		PhH DMSO[c]	2 4		96 (88) 99
		PhH	2		99
	$C_5H_{11}CH=CH_2$	PhH	2		30
		DMSO[c]	4		73
		DMSO[c]	4		81
		PhH	6		48[d]
		PhEt[e]	2		65
	$C_6H_{13}C\equiv CH$	PhEt[e]	2		34
		PhH	2		(80)
		PhH	2		(59)
		PhH	23		(26)

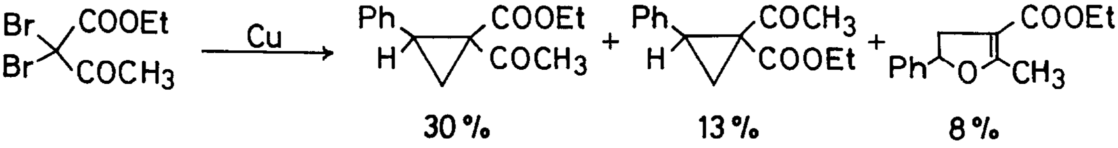
a. Reactions were normally carried out with dibromodiketone (1.5 mmol), copper powder (3.0 mmol), and olefin or acetylene (1.0 mmol) in the presence (in PhH) or absence (in DMSO) of iodine (0.05 mmol) at 70-80 °C (in PhH) or 20-30 °C (in DMSO). b. Determined by VPC, based on the olefin or acetylene. Yields in parentheses are isolated yields. c. The amount of copper powder employed was 1.50 mmol. d. E/Z = 60/40. e. Ethylbenzene was used as solvent at reflux.

Although cyclic dibromodiketones gave the corresponding dihydrofurans or furans smoothly, reactivities of acyclic dibromodiketones were low. For example, the reaction of 3,3-dibromo-2,4-pentanedione with styrene gave the corresponding dihydrofuran derivative only in 26% yield. 2,2-Dibromo-1,3-diphenyl-1,3-propanedione did not afford the cycloadduct.[3] The reason is not clear at present.

While we have been preoccupied with synthetic aspects of the present reaction, the following observations seem to be important from a mechanistic point of view. (1) Copper metal was converted into γ-copper(I) bromide[4] (in benzene) or copper(II) bromide-DMSO complex[5] (in DMSO), indicating that copper metal acted as a reductive debrominating agent.[6] (2) Lack of stereospecificity in the reaction of (Z) and (E)-β-methylstyrene suggests a non-concerted mechanism.[7]



(3) The reaction of ethyl dibromoacetoacetate with styrene and copper gave both dihydrofuran and cyclopropane derivatives. However, the latter did not rearrange to the former under the reaction conditions implying direct formation of dihydrofuran ring rather than isomerization of initially produced cyclopropane to dihydrofuran.[8,9]



By virtue of high regioselectivity, mild reaction conditions, and simple procedure, the present reaction provides a useful route to dihydrofuran[10] and furan[11] derivatives from olefins and acetylenes. Further work is now in progress to explore full range of scope and limitations of this useful cycloaddition reaction and to elucidate the mechanistic details.

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(2) Ketocarbenoid was generated by reductive α-elimination of dibromoketone with zinc, see (a) Scott, L. T.; Cotton, W. D. *J. Am. Chem. Soc*. 1973, 95, 2708. (b) Scott, L. T.; Cotton, W. D. *ibid*. 1973, 95, 5416. See also ref. 8.

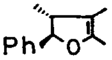
(3) Dibromodiketone and copper were consumed during the course of the reaction, but the corresponding dihydrofuran or cyclopropane derivatives were not detected.

(4) Identified by X-ray powder data.

(5) Identified by comparison of its IR spectrum with that of an authentic sample. Meek, D. W.; Sttaub, D. K.; Drago, R. S. *J. Am. Chem. Soc*. 1960, 82, 6013.

(6) Kawabata, N.; Kamemura, I.; Naka, M. *J. Am. Chem. Soc*. 1979, 101, 2139 and references cited therein.

(7) The stereochemistry of the product was clearly assigned as trans based on ^{1}H NMR data. The methyl group at δ = 1.35 compared more favorably with δ = 1.12 of C-4 methyl of trans compound A[9a] than with δ = 0.50 of cis compound B,[9a] in which the cis methyl group is shielded by the phenyl group. See also ref. 9b.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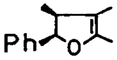
B

(8) Ketocarbenoid generated by α-elimination of ω,ω-dibromoacetophenone with copper was trapped by olefin to form cyclopropane derivative. Kawabata, N.; Fujii, T.; Naka, M. Yamashita, S. *Bull. Chem. Soc. Jpn*. 1977, 50, 1005.

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