Alkenylcopper Derivatives; 22[1,2]. Stereoselective Synthesis of Allylic Thioethers

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Allylic thioethers are useful intermediates in synthetic organic chemistry. The are used as such as electrophiles[3,4,5], or in a higher oxidation state (sulfonium salts[3], sulfoxides[6], or sulfones[5-8]) for substitution by various organometallic reagents or metal enolates. They are also used as nucleophiles, after metallation by alkyllithium at the allylic position[9,10]. They can also serve in other synthetic reactions such as the thio-Claisen rearrangement[11,12].

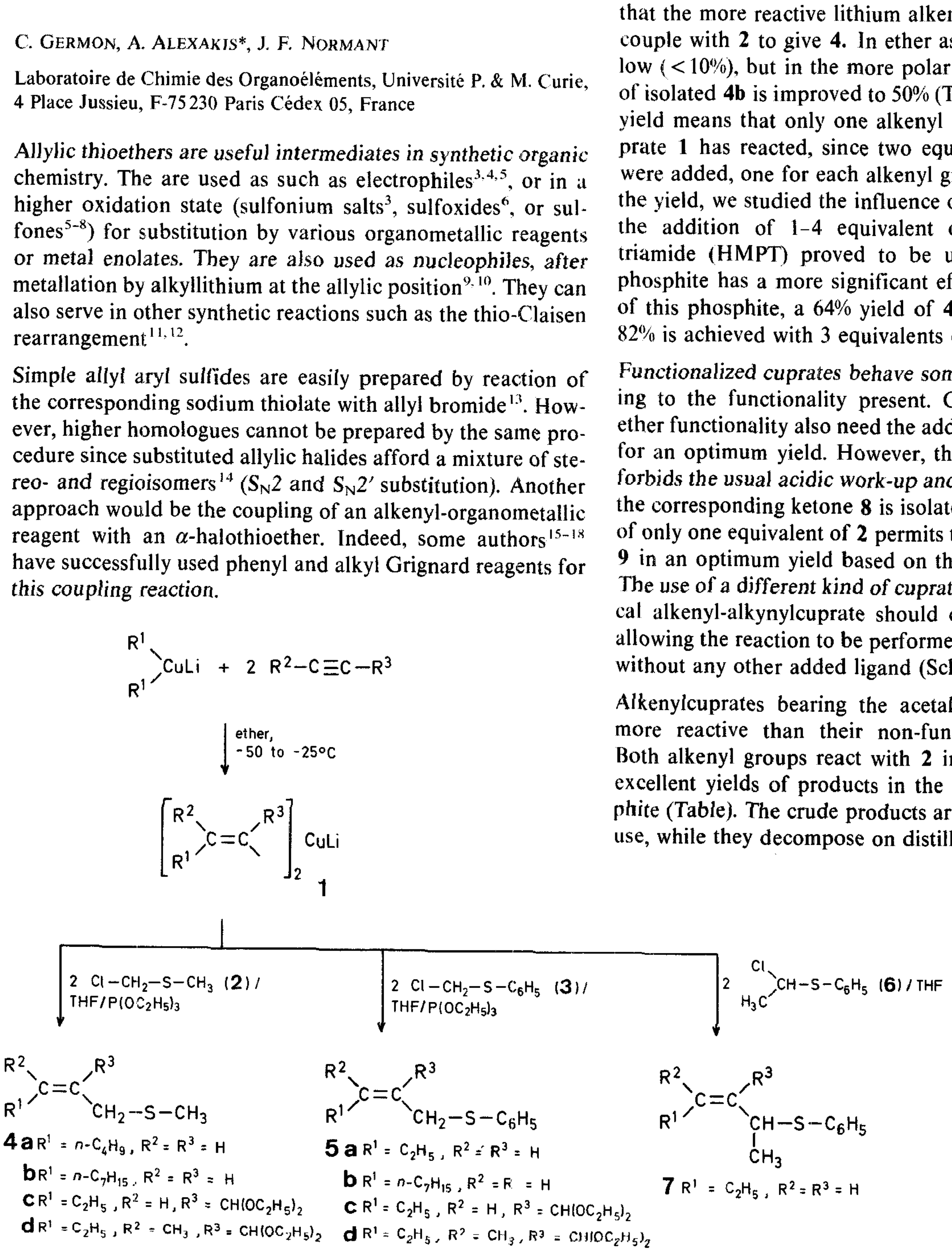
Simple allyl aryl sulfides are easily prepared by reaction of the corresponding sodium thiolate with allyl bromide[13]. However, higher homologues cannot be prepared by the same procedure since substituted allylic halides afford a mixture of stereo- and regioisomers[14] (S_N2 and S_N2' substitution). Another approach would be the coupling of an alkenyl-organometallic reagent with an α-halothioether. Indeed, some authors[15-18] have successfully used phenyl and alkyl Grignard reagents for this coupling reaction.

We have found that alkenyl-cuprate and -copper reagents **1** and **10** also undergo such a reaction and may be used for the synthesis of a variety of allylic thioethers **4, 5, 7, 9, 11, 14** with a defined substitution pattern. These alkenyl-cuprate and -copper reagents **1** and **10** are easily available by the carbocupration reaction of alkynes with alkyl-copper or -cuprate derivatives[19]. For this study we have used two typical thiomethylation reagents namely, the commercially available α-chloromethyl methyl sulfide **(2)** and the chloromethyl phenyl sulfide **(3)**, which is easily prepared in bulk by reaction of sulfuryl chloride with thioanisole[17].

In a preliminary result it was shown that an alkenylcopper reagent associated with a magnesium salt, **10**, was able to couple with **2** under the standard alkylation conditions (3 equivalents of triethyl phosphite plus 4 equivalents of hexamethylphosphoric triamide)[20]. Further work has now shown that the more reactive lithium alkenylcuprate reagents **1** also couple with **2** to give **4**. In ether as solvent the yield is quite low (< 10%), but in the more polar tetrahydrofuran the yield of isolated **4b** is improved to 50% (Table and Scheme **A**). This yield means that only one alkenyl group of the dialkenylcuprate **1** has reacted, since two equivalents of electrophile **2** were added, one for each alkenyl group. In order to improve the yield, we studied the influence of various additives. Thus, the addition of 1-4 equivalent of hexamethylphosphoric triamide (HMPT) proved to be useless. However, triethyl phosphite has a more significant effect. With one equivalent of this phosphite, a 64% yield of **4b** is obtained. A yield of 82% is achieved with 3 equivalents of this reagent (Table).

Functionalized cuprates behave somewhat differently according to the functionality present. Cuprates bearing an enol ether functionality also need the addition of triethyl phosphite for an optimum yield. However, the enol ether functionality forbids the usual acidic work-up and instead of the enol ether, the corresponding ketone **8** is isolated. However, the addition of only one equivalent of **2** permits the isolation of the sulfide **9** in an optimum yield based on the chloromethyl sulfide **2**. The use of a different kind of cuprate, namely an unsymmetrical alkenyl-alkynylcuprate should circumvent this difficulty allowing the reaction to be performed in only tetrahydrofuran without any other added ligand (Scheme **B**).

Alkenylcuprates bearing the acetal functionality are much more reactive than their non-functionalized counterparts. Both alkenyl groups react with **2** in tetrahydrofuran to give excellent yields of products in the absence of triethyl phosphite (Table). The crude products are pure enough for further use, while they decompose on distillation.

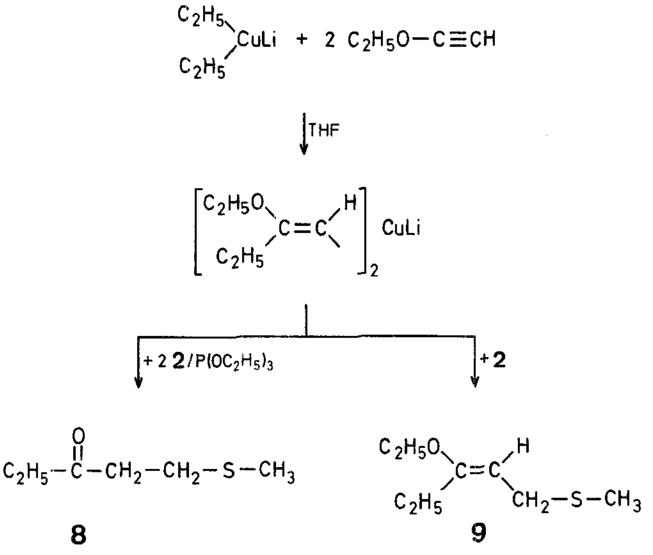


4a $R^1 = n\text{-}C_4H_9$, $R^2 = R^3 = H$
b $R^1 = n\text{-}C_7H_{15}$, $R^2 = R^3 = H$
c $R^1 = C_2H_5$, $R^2 = H$, $R^3 = CH(OC_2H_5)_2$
d $R^1 = C_2H_5$, $R^2 = CH_3$, $R^3 = CH(OC_2H_5)_2$

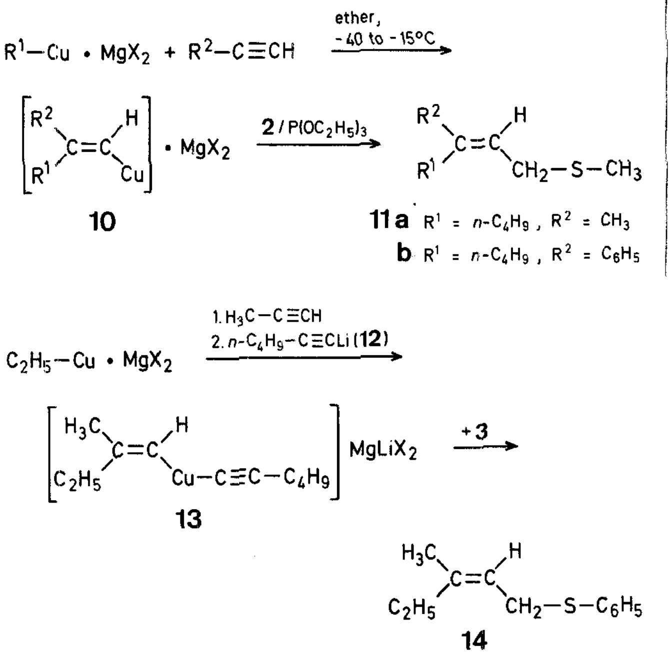
5a $R^1 = C_2H_5$, $R^2 = R^3 = H$
b $R^1 = n\text{-}C_7H_{15}$, $R^2 = R^3 = H$
c $R^1 = C_2H_5$, $R^2 = H$, $R^3 = CH(OC_2H_5)_2$
d $R^1 = C_2H_5$, $R^2 = CH_3$, $R^3 = CH(OC_2H_5)_2$

7 $R^1 = C_2H_5$, $R^2 = R^3 = H$

Scheme A



Scheme B



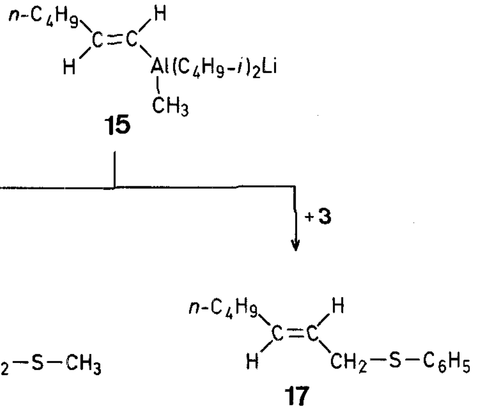
Scheme C

Alkenylcopper reagents associated with a magnesium salts, **10**, are less reactive than the corresponding cuprates **1**. The reaction without any added reagent affords a low yield of coupling products **11b** (Table). However, upon addition of 3 equivalents of triethyl phosphite the yield is improved, while the addition of HMPT does not improve the yield, as previously reported[20].

Chloromethyl phenyl sulfide (**3**) behaves quite differently. This compound is prone to deprotonate with organometallic reagents to afford a carbene. Lithium (*Z*)-dialkenylcuprates **1** react with 2 equivalents of **3** in tetrahydrofuran to give the allylic sulfide **5** isolated in 65–67% yield (Table). Here both the alkenyl groups have reacted without the need of any additive. Indeed, addition of HMPT or triethyl phosphite did not improve the yield.

Functionalized cuprates behave similarly, and in all cases, an excellent yield of product is again obtained (Table). The reactivity of alkenylcopper reagents associated with a magnesium salt, **10**, is quite different. No coupling product is observed in ether or tetrahydrofuran even with added reagents such as HMPT or triethyl phosphite. The only successful way to obtain the desired allylic sulfide is to transform, first, the alkenylcopper reagent into the more reactive cuprate species **13** by addition of a lithium acetylenide **12** (Scheme **C**). Under these conditions a 64% yield of the coupling product **14** is obtained (Table). The coupling reaction may also be extended to substituted α-chloroalkyl phenyl sulfides such as **6**[21] (Scheme **A**) to give **7**.

The corresponding (*E*)-isomers of the allylic sulfides **4** and **5** were also prepared for comparison purposes. This is exemplified by the reaction of (*E*)-trialkylalkenyllithium alanate **15**[22,23] with the chlorosulfides **2** and **3** to give the allylic sulfides **16** and **17** (Scheme **D**).



Scheme D

With both the (*Z*)- and (*E*)-isomers in hand, we were able to determine by capillary gas chromatography (OV 101, 25 m) that the (*Z*)-isomer has a stereoisomeric purity higher than 99.8% and that the (*E*)-isomer is >99.5% pure. These degrees of purity are well in accordance with the usual stereoselectivity observed in the carbocupration reaction as well as with the hydroalumination reaction of alkynes.

Thus, we disclose a general methodology for the synthesis of allylic sulfides with a very high stereoisomeric purity. These sulfides may also bear another functionality which makes them attractive for the synthesis of more elaborated molecules.

(*Z*)-Alkenyl Methyl Thioethers 4, 5, 7, 9, 11, 14; General Procedure: An ether or tetrahydrofuran solution of lithium dialkenylcuprate **1** (25 mmol in 100 ml of solvent) or alkenylcopper reagent **10** (50 mmol) is prepared according to the standard procedure[19]. If the reagent is prepared in ether, tetrahydrofuran (50 ml) is added at −30°C, followed by either hexamethylphosphoric triamide or triethyl phosphite (see Table) or 1-lithio-1-hexyne (**12**; 50 mmol). The appropriate α-chloromethyl sulfide **2**, **3**, or **6** (50 mmol; 25 mmol for obtaining **9**) is added and the resulting mixture stirred for 4 h at room temperature and then hydrolyzed at −10°C with 5 normal hydrochloric acid (80 ml). Product mixtures containing an acid-sensitive functionality are decomposed with ammonium chloride solution (50 ml). After filtration, the organic layer is washed with dilute ammonia (10 ml), ammonium chloride solution (40 ml), dried with magnesium sulfate or potassium carbonate, and evaporated. The residue obtained is purified by distillation using a 10 cm Vigreux column.

In the case of dialkenylcuprate carrying an enol ether moiety, the hydrolyzed product obtained could not be separated from triethyl phosphite by distillation. However, column chromatography on silica gel (eluent: 20:1 hexane/ethyl acetate) affords instead of the expected enol ether, the corresponding ketone **8**, which is identified by spectral data.

Table. Allylic Thioethers **4**, **5**, **7**, **9**, **11**, and **14** prepared

Product	Additive (mol.-equiv.)	Yield [%][a]	b.p. [°C]/ torr	n_D^{20}	Molecular formula[b]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/ TMS)[c,f] δ [ppm]	^{13}C-N.M.R. (CDCl$_3$/ TMS)[d,f] δ [ppm]
4a	$P(OC_2H_5)_3$ (3)	78	76°/15	1.4759	$C_8H_{16}S$ (144.3)	1650	2.02 (s, 3H); 3.10 (d, 2H); 5.54 (m, 2H)	14.5; 31.9; 125.3; 132.8
4b	—	50	70°/0.01	1.4712	$C_{11}H_{22}S$ (186.4)	1650	1.92 (s, 3H); 3.04 (d, 2H); 5.45 (m, 2H)	14.5; 30.3; 125.2; 132.9
	HMPT (2)	50						
	$P(OC_2H_5)_3$ (3)	82						
4c	—	92	67°/0.01	1.4701	$C_{11}H_{22}O_2S$ (218.4)	1655; 1050	2.04 (s, 3H); 3.20 (s, 2H); 3.52 (m, 4H); 4.94 (s, 1H); 5.84 (t, 1H)	15.5; 30.0; 61.6; 101.7; 131.6; 133.1
4d	—	74	—[e]	—	—	—	1.77 (s, 3H); 2.05 (s, 3H); 2.18 (q, 2H); 3.16 (s, 2H); 3.28 (s, 6H); 4.91 (s, 1H)	—
5a	—	67	75°/0.01	1.5590	$C_{11}H_{14}S$ (178.3)	3030; 3010	3.44 (d, 2H); 5.40 (m, 2H); 7.08-7.24 (m, 5H)	31.2; 123.9; 135.1
	HMPT (2)	47						
	$P(OC_2H_5)_3$ (3)	60						
5b	—	65	98°/0.01	1.5241	$C_{16}H_{24}S$ (248.4)	3060; 3040; 1650; 1590; 735; 690	3.46 (d, 2H); 5.42 (m, 2H); 7.05-7.22 (m, 5H)	31.3; 124.4; 135.6
5c	—	99	—[e]	—	—	—	2.01 (m, 2H); 3.57 (s, 2H); 4.88 (s, 1H); 5.74 (t, 1H); 7.20-7.37 (m, 5H)	—
5d	—	90	—[e]	—	—	—	1.79 (s, 3H); 2.17 (q, 2H); 3.29 (s, 6H); 3.64 (s, 2H); 4.95 (s, 1H); 7.14-7.32 (m, 5H)	—
7	—	53	67°/0.01	1.4686	$C_{12}H_{16}S$ (192.3)	3060; 3010; 1650; 1585; 750; 690	1.28 (d, 3H); 4.02 (m, 1H); 5.24 (m, 2H); 7.24-7.38 (m, 5H)	21.3; 41.6; 127.2; 132.4
9	—	76	84°/15	1.4818	$C_8H_{16}OS$ (160.3)	1655; 1090	2.05 (s, 3H); 3.21 (d, 2H); 3.89 (q, 2H); 4.56 (t, 1H)	14.6; 31.2; 62.1; 92.5; 160.6
11a	$P(OC_2H_5)_3$ (3)	56	86°/15	1.4779	$C_9H_{18}S$ (158.3)	1660	1.72 (s, 3H); 1.96 (s, 3H); 3.02 (d, 2H); 5.20 (t, 2H)	14.7; 23.4; 31.1; 31.5; 120.8; 139.3
11b	$P(OC_2H_5)$ (3)	61	109°/0.01	1.5430	$C_{14}H_{20}S$ (220.4)	3080; 3060; 765; 700	3.20 (d, 2H); 5.69 (t, 1H); 7.12-7.28 (m, 5H)	14.7; 31.6; 126.3; 143.2
	—	33						
14	n-$C_4H_9{-}C{\equiv}CLi$ (1)	64	91°/0.1	1.5496	$C_{12}H_{16}S$ (192.3)	3060; 1655	1.74 (s, 3H); 3.58 (d, 2H); 5.38 (t, 1H); 7.2-7.4 (m, 5H)	31.7; 118.9; 141.7

[a] Yield of isolated product.

[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.24; exceptions: **4d, 5c, 5d** which could not be distilled.

[c] JEOL MH 100 spectrometer.

[d] JEOL FX 900 spectrometer.

[e] Partial decomposition occurs during distillation; products identified by ^{1}H-N.M.R. spectrometry.

[f] ^{1}H- and ^{13}C-N.M.R. assignments available on request to the authors.

Methyl 3-Oxopentyl Thioether (8):

I.R. (Neat): $\nu = 1715, 1190$ cm^{-1}; n_D^{20}: 1.4709.

^{1}H-N.M.R. (CDCl$_3$/TMS): $\delta = 2.12$ (s, 4H, $CO{-}C\underline{H}_2{-}C\underline{H}_2{-}S$); 2.46 (q, 2H, $C\underline{H}_2CH_3$); 2.72 ppm (s, 3H, $S{-}C\underline{H}_3$).

^{13}C-N.M.R. (CDCl$_3$/TMS): $\delta = 15.7$ ($CO{-}\underline{C}H_2CH_2S$); 209.3 ppm ($\underline{C}{=}O$).

(*E*)-Alkenyl Methyl Thioethers 16, 17; General Procedure:

An hexane solution of (*E*)-dialkylalkenylalane **15** (30 mmol) is prepared from 1-hexyne (2.46 g, 30 mmol) and a 1 molar hexane solution of diisobutylaluminium hydride (30 mmol) according to the usual procedure[22]. This solution is diluted with tetrahydrofuran (50 ml) at 0°C and then a 1 molar ether solution of methyllithium (50 ml, 50 mmol) is added. To the white suspension of alanate obtained[23] is added the α-chloromethyl sulfide **2** or **3** (30 mmol) and the mixture is stirred at room temperature for 4 h. After hydrolysis with 10% aqueous sulfuric acid (50 ml) and filtration, the organic phase is washed with sodium sulfate solution (2 × 50 ml), dried with magnesium sulfate, and the solvent evaporated. The residue obtained is purified by distillation.

The authors gratefully acknowledge support from the Centre National de la Recherche Scientifique (E.R.A. 825).

Received: July 18, 1983

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