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From 2-thienylcopper couplings to trimethylsilyl-promoted organocopper additions

Eva-Lotte Lindstedt, Martin Nilsson* and Thomas Olsson

Department of Organic Chemistry, Chalmers University of Technology, S-412 96 Göteborg (Sweden)

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Abstract

In this paper we continue a 2-thienylcopper line started about twenty years ago with the cross-coupling with iodobenzenes in quinoline. We now report a preparative and NMR study of the favourable influence of trimethylchlorosilane on the conjugate addition of lithium methyl(2-thienyl)cuprate to methyl cinnamate and of 2-thienylcopper and butylcopper to 4-phenyl-3-propen-2-one.

NMR spectra of lithium methyl(2-thienyl)cuprate in tetrahydrofuran show the presence of two different organocuprate species (**A** and **B**). Trimethylchlorosilane strongly favours conjugate addition to methyl cinnamate at even −60 °C and also favours form **B** (then presumably complexed by TMSCl). Thus again 2-thienylcopper has proved itself as a practical and illustrative tool in organocopper chemistry.

We have chosen to report here some recent NMR and preparative results of the favourable action of trimethylchlorosilane on the conjugate addition of lithium methyl(2-thienyl)cuprate to methyl cinnamate against a background on our earlier thienylcopper work.

Earlier thienylcopper work

During the early exploration of arylcopper chemistry we observed the selective and unsymmetrical coupling of a 2-thienylcopper reagent with iodobenzene in quinoline to give 2-phenylthiophenes [1,2]. We saw this reaction as an organometallic extension of the classical Ullmann biaryl synthesis [3]. During the attempted generalisation of this coupling we and others noted that arylcopper compounds and iodoarenes could sometimes undergo copper–iodine exchange, which could interfere with the cross-coupling reaction [4]. Copper–halogen exchange poses corresponding problems in cross-coupling with organocuprates [5,6]:

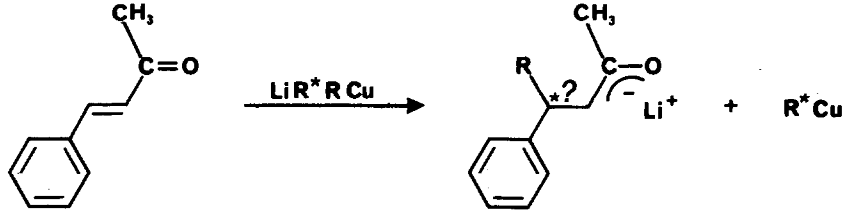
2-Thiophenecarboxylic acid is readily decarboxylated and undergoes copper-promoted decarboxylative coupling with iodoarenes in quinoline (L), possibly via 2-thienylcopper [7], in analogy with the decarboxylative coupling of 2-nitrobenzoic acids [8]:

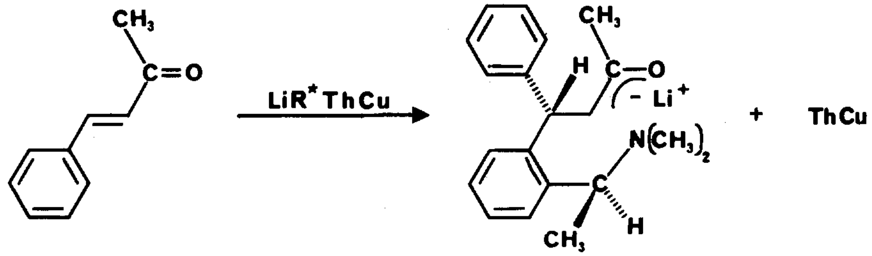
$$\mathrm{ArCOOCu{\cdot}L} \xrightarrow{-\mathrm{CO_2}} \left[\mathrm{ArCu{\cdot}L}\right]^{?} \xrightarrow{\mathrm{Ar'I}} \mathrm{Ar{-}Ar'}$$

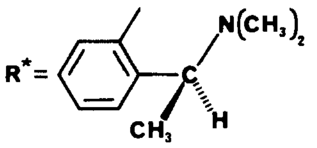
Ar: 2-nitrophenyl, 2-thienyl, 2-furyl

During more recent work on conjugate addition to enones and enolates we tried to use the 2(1-dimethylaminoethyl)phenyl group (R*) as a chiral auxiliary in mixed lithium diorganocuprates LiRR*Cu [reviewed in ref. 9]. The group was a good auxiliary in the sense that the other group (alkyl, phenyl, 2-pyridyl) could be added and that 2(1-dimethylaminoethyl)phenylcopper (R*Cu) was regenerated, but the enantioselectivities were very low.

However, the attempted addition of the 2-thienyl group to enones with lithium [2(1-dimethylaminoethyl)phenyl]cuprate was unsuccessful, instead the 2(1-dimethyl-







aminoethyl)phenyl group was added and 2-thienylcopper was regenerated. The addition gave practically only one diastereomer, the same product as that from the addition of lithium bis[2-(1-dimethylaminoethyl)]phenylcuprate, namely the thermodynamically most favourable lithium enolate [10,11].

Thus by a serendipious observation the 2-thienyl group returned to the scene, now as a good auxiliary in mixed cuprates for diastereoselective additions of the chiral 2(1-dimethylaminoethyl)phenyl group. Following this clue we have also reported that mixed lithium organo(2-thienyl)cuprates, "LiRThCu", are often useful in conjugate additions adding the organo group to enones and enolates with regeneration of 2-thienylcopper. Such mixed cuprates are rather stable, easy to handle even at 0 °C and somewhat less reactive than the corresponding lithium diorganocuprate [12]. Lipshutz has developed the use of the 2-thienyl group also in the higher order, mixed lithium organocuprates [13].

Trimethylchlorosilane and organocopper reagents

The increased use of trimethylchlorosilane (TMSCl) to trap the enolates from lithium organocuprate additions has been reviewed by Taylor [14]. Corey and Boaz [15] as well as Alexakis, Berlan and Besace [16] recently have shown that trimethylchlorosilane improves and accelerates conjugate additions with lithium diorganocuprates to α,β-unsaturated carbonyl compounds. Very recently the use of trimethylchlorosilane, particularly in combination with hexamethylphosphoric triamide or 4-dimethylaminopyridine, has been shown to promote the conjugate additions of lithium dibutylcuprate, lithium diphenylcuprate and butylcopper in THF [17].

We have now observed considerable improvements with trimethylchlorosilane in the reactions of lithium organo(2-thienyl)cuprates and have been able to study the reagents and the reactions with proton and carbon-13 NMR spectrometry. The methyl cinnamate/lithium methyl(2-thienyl)cuprate couple provided an illustrative system since the NMR spectra are reasonably simple and the reaction without TMSCl is conveniently slow.

Present results

Lithium methyl(2-thienyl)cuprate in tetrahydrofuran does not add its methyl group to methyl cinnamate at 0 °C. Instead, according to NMR spectra, it forms a rather stable π complex, analogous to that recently described for lithium dimethylcuprate [18]. However, in the presence of trimethylchlorosilane conjugate addition occurs rapidly even at −60 °C to produce primarily the lithium enolate of methyl 3-phenylbutanoate.

The reaction in ether (at 0 °C without TMSCl) gives a 45% yield [12]. When trimethylchlorosilane is added (−50 °C) the practical isolated yield increases to 75%. The amount of higher condensation products (dimers/trimers) is lower than in the usual conjugate additions, trimethylsilylthiophene is a new but minor by-product. As long as reagents and substrate are mixed at low temperatures (below −30 °C) the order of addition has little influence on the practical outcome of the reaction. The mixture of TMSCl and LiMeThCu was more stable at 0 °C than mixtures of lithium dimethylcuprate and TMSCl, which rapidly give tetramethylsilane.

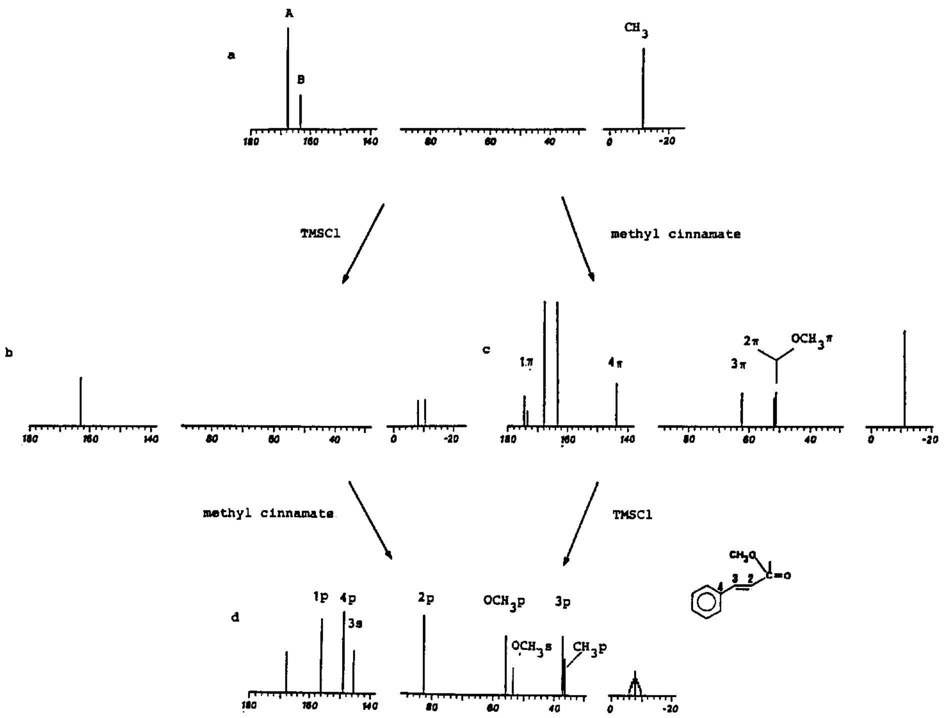
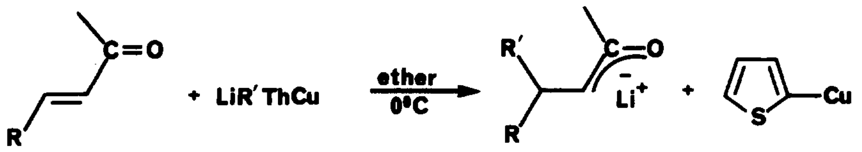


Fig. 1. Schematic NMR spectra for addition of lithium methyl(2-thienyl)cuprate to methyl cinnamate. (a) Part of the ^{13}C NMR spectrum of the cuprate in THF-d_8 at −50 °C. A and B represent the quaternary carbon in the thienyl group in the reagents A and B present. (b) Addition of one equivalent of TMSCl to the NMR tube (−60 °C). (c) Addition of 0.25 equivalent of methyl cinnamate to the NMR tube (−60 °C). (d) Addition of 0.25 equivalent of methyl cinnamate and one equivalent of TMSCl (to the NMR tube at −60 °C). The shift of 2s is 118 ppm, the peak at −8 (ppm) is very broad; π stands for π complex, p for product and s for substrate.

The NMR spectra of the cuprates and the reaction mixtures are complex. Some features, however, are prominent and facilitate the interpretation, particularly the methyl signals and the signals of the 2-carbon of the thienyl group. Figure 1 gives a simplified account of the species observed.



^{1}H and ^{13}C NMR spectra of the lithium methyl(2-thienyl)cuprate in THF-d_8 clearly demonstrate the existence of two different organocuprate species, present in unequal amounts. At −50 °C one of them, A, predominates. When trimethylchlorosilane is added the signals broaden indicating a rapid interconversion of these two species; the coalescence temperature is −52 °C. Below this temperature (at −60/68 °C) the pattern sharpens again and now a species very similar to the previous minority form (B) predominates. The coordinated TMSCl in the cuprate (as well as in the 2-thienylcopper) reagent gave separate ^{1}H NMR signals at about δ 0.2 ppm, thus slightly upfield from TMSCl, and also a new signal in the ^{29}Si NMR spectrum [21].

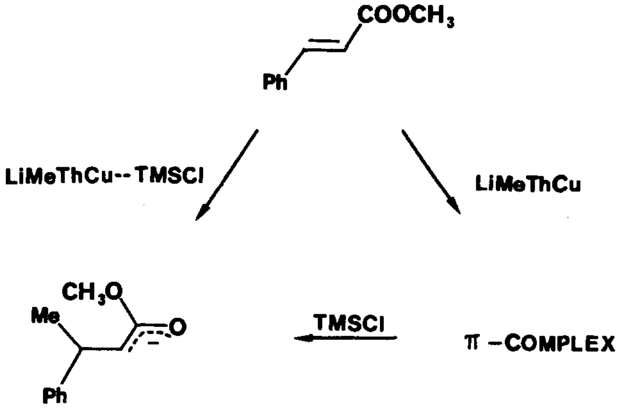
Methyl cinnamate added at this low temperature reacts rapidly with form **B** giving an enolate of the conjugate addition product whereas form **A** forms a fairly stable π complex with methyl cinnamate. If methyl cinnamate is first added to lithium methyl(2-thienyl)cuprate the π complex is formed and subsequent addition of trimethylchlorosilane starts conjugate addition. The temperatures indicated above were chosen to provide clear NMR observations. For preparative purposes we could recommend a temperature below −30 °C. Further work has showed that also other groups can be added to the methyl cinnamate and to benzalacetone with LiRThCu and TMSCl [19].

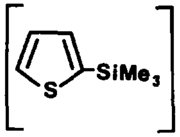
Stimulated by the power of the trimethylchlorosilane-promoted reaction we also checked the reactivities of an alkyl- and an aryl-copper. We found that 2-thienylcopper or butylcopper in ether add to benzalacetone to give the TMS enol ethers (both *E* and *Z* forms) of the conjugate adducts in fair yields [20].

Discussion, conclusions

The activation of organocuprates and of alkyl- and aryl-copper reagents by TMSCl provides new dimensions of organocopper chemistry, preparatively and mechanistically. Using the relatively stable lithium methyl(2-thienyl)cuprate as a probe (and with limited results in hand) we can now only indicate some possibilities.

The NMR data indicate that two species (**A** and **B**) are present in the THF solution of the lithium methyl(2-thienyl)cuprate reagent as measured at −50 °C. The reagent immediately and reversibly gives a π complex with methyl cinnamate, leaving some of species **B** in solution. Cuprate species **B** is favoured by TMSCl,





apparently by complex formation (**B**...TMSCl). The NMR spectral characteristics of **B** change little on complexation with TMSCl. The TMSCl-activation works both with the organocuprate and with the organocopper compounds.

This evidence taken together indicates an interaction between the copper and the TMSCl with activation and polarisation of the carbon–copper bond. Such an interaction could provide a better pathway towards interaction of copper with the carbon–carbon double bond in the α,β-unsaturated carbonyl compound and also for formation of trimethylsilylthiophene.

Thus we hope that the continued work with thienylcopper will provide answers to some of the many questions in the organocopper field, and perhaps also to the relations between conjugate addition and cross-coupling.

Experimental

All reactions were performed under argon with dry equipment. Diethyl ether was distilled from sodium benzophenone ketyl. Commercial (Aldrich) butyllithium in hexane and methyllithium in ether were used. Copper iodide was purified via potassium diiodocuprate. The NMR experiments were performed in commercial THF-d_8. The reaction mixtures were hydrolysed by addition of aqueous ammonia/ammonium chloride at pH 8 and extracted two or three times with ether. Low temperature ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL 400 spectrometer. The products were characterized by gas chromatography (HP 5880, OV 17), gas chromatography/mass spectrometry (Finnigan 1020, capillary column) and ^{1}H NMR (Bruker WH 270).

Lithium methyl(2-thienyl)cuprate. Butyllithium (2.5 mmol) was added to a solution of thiophene (3 mmol) in ether (5 ml) at 0 °C and the solution was stirred at room temperature for at least 40 min. Then another 2.5 ml ether was added, the mixture was cooled in an icebath, and finally powdered copper iodide (2.5 mmol) was added. 2-Thienylcopper formed immediately as a yellowish suspension. The mixture was stirred for about five min and then methyllithium (4.85–4.95 mmol) was added. Then the mixture was stirred until the Gilman test for free alkyllithium [22] was negative (about 5 min). The colour of the cuprate solution is either yellow or light green. The reaction mixture was then cooled to about −50 °C and methyl cinnamate (2 mmol) in ether (2.5 ml) was added. The addition resulted in a shiny yellow colour. Within one minute from the substrate addition trimethylchlorosilane (TMSCl) (5 mmol) was added. The temperature was allowed to rise to 0 °C and the reaction was followed by GLC. After work-up the crude product dissolved in pentane was chromatographed through silica gel in order to separate trimethylsilylthiophene from the conjugate adduct. The silica gel was then eluted with ether. After filtration, drying with sodium sulfate and evaporation the yield was 0.268 g (75%) of methyl (3-phenyl)butanoate.

NMR samples. Lithium methyl(2-thienyl)cuprate (generally 1 mmol) was prepared as described above. Diethyl ether was evaporated in vacuum (0 °C, room temperature). The residue was dissolved in THF-d_8 (0.5–1 ml) and the solvent was evaporated once again in order to replace diethyl ether bonded to the cuprate by THF. Finally THF (1 ml) was added and the sample transferred to the NMR tube via a stainless steel tube. TMSCl and methyl cinnamate were added to the NMR tube at the NMR spectrometer. The shift of THF was used as reference ^{1}H NMR 3.65 ppm and ^{13}C NMR 68.6 ppm.

In a separate control experiment a large portion of the ether was evaporated, some THF added (as lock and reference) and the carbon-13 spectrum was recorded. The essential features were the same as those of the THF solution, although some broadening indicated dynamic processes.

Acknowledgement

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