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Preliminary communication

AN ORGANOMETALLIC ROUTE TO (±)-3-*p*-TOLUENESULFINYL-2-PYRONE

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Summary

3-Bromo-2-pyrone reacts with dimethylcopperlithium and then with *p*-tolyl *p*-toluenethiosulfonate to form 3-*p*-toluenethio-2-pyrone. Organocopper species are likely intermediates in this reaction. Oxidation of the sulfide produces (±)-3-*p*-toluenesulfinyl-2-pyrone. The overall process involves an important and useful umpolung, a reversal of reactivity at C(3) of the pyrone ring from an electrophilic center to a nucleophilic center.

As part of our research program on the use of enantiomerically pure unsaturated ketone and lactone sulfoxides for asymmetric carbon—carbon bond formation with various organometallic reagents [1], we required (+)- or (—)-3-*p*-toluenesulfinyl-2-pyrone (**3**). Because even racemic pyrone sulfoxide **3** had not been made before, we chose to prepare the racemate and to investigate its chemistry before attempting the more difficult task of preparing enantiomerically pure (+)- or (—)-**3**. We report here a reliable and very short (3-step, 2-pot) synthesis of (±)-**3** involving organocopper intermediates.

3-Bromo-2-pyrone (**1a**) was prepared via bromination—dehydrobromination of 2-pyrone [2] using a slightly modified (40 h instead of 24 h reflux, 1.4/1 molar ratio of pyrone/carbon tetrachloride; 59% overall yield from 2-pyrone) literature procedure [3]. Attempts at direct bromine → lithium exchange [4], (i.e. at formation of 3-lithiopyrone **1b**) using n-butyllithium at —78°C failed, giving only what appeared to be n-butyl addition products [5]. In contrast, bromine → copper exchange was highly successful.

Treating 3-bromo-2-pyrone (**1a**) with 2 equivalents of dimethylcopperlithium in diethyl ether at —78°C led, after 2 h, to complete bromine → copper exchange; hydrolytic work-up gave 2-pyrone in good yield, with less than 5% of the coupling product [6] 3-methyl-2-pyrone being formed. A mechanistic

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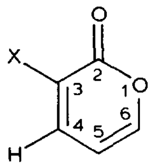
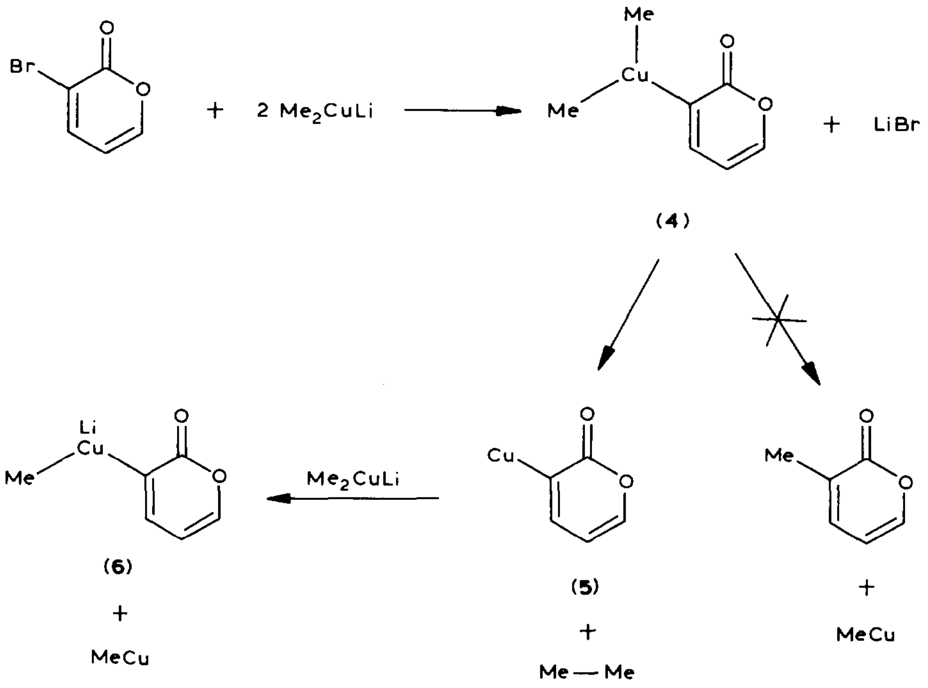


(**1a**, X = Br; **1b**, X = Li;
2, X = *p*-TolS;
3, X = $p\text{-Tol}\overset{\text{O}}{\overset{\|}{\text{S}}}$)

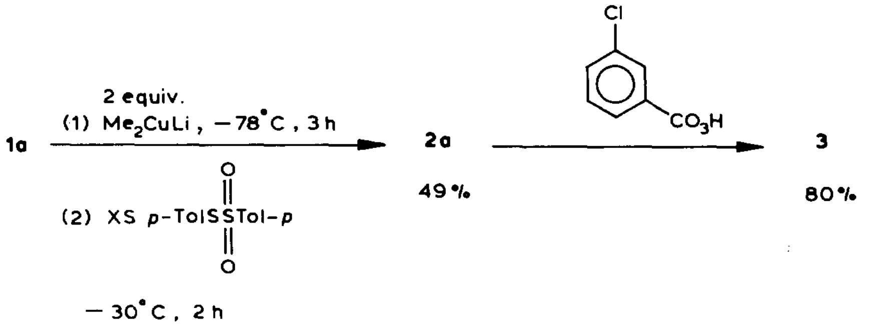
rationalization of this result is shown in Scheme 1 involving transient copper(III) intermediate **4** which apparently undergoes selective reductive elimination of ethane (rather than of 3-methyl-2-pyrone) to form a 3-cuprio-2-pyrone (e.g. **5**); the excess dimethylcopperlithium might react with cuprio-pyrone **5** to form a more reactive cuprate species (e.g. **6**) and possibly methylcopper (a yellow-green precipitate is initially observed) [7]. Similar bromine → copper exchanges instead of carbon—carbon couplings are known during reaction of organocopper reagents with some α-bromoketones [8], α-bromoacrylate esters [9], and alkenyl bromides [10]; it has been possible in these cases to intercept the newly-formed organocopper species with a limited number of electrophiles either intermolecularly [8,9] or intramolecularly [10].



SCHEME 1

When 3-bromo-2-pyrone (1a) reacts with dimethylcopperlithium at —78°C for 3 h and then with *p*-tolyl *p*-toluenethiosulfonate [11] at —30°C for 2 h, a coupling reaction occurs to form 3-*p*-tolylthio-2-pyrone (2, ^{1}H, NMR ($CDCl_3$): δ 6.54 (dd, 1H, H_4)) isolated after preparative TLC in 49% yield (based on bromopyrone 1a, eq. 1). Standard oxidation of sulfide 2 produces the desired, racemic, crystalline, lactone sulfoxide 3 (m.p. 112—113°C; ^{1}H NMR ($CDCl_3$): δ 8.08 (dd, 1H, $J_{4,5}$ 6.7 Hz, $J_{4,6}$ 2.1 Hz, H_4). Analysis: found: C, 61.52; H, 4.30; S, 13.69; $C_{12}H_{10}O_3S$ calcd.: C, 61.60; H, 4.31; S, 13.61%).

It is noteworthy that a C(3)-tolylthio group causes an upfield chemical shift of H(4) comparable to that caused by a C(3)-methoxy group, whereas a C(3)-tolylsulfinyl group causes a downfield chemical shift of H(4) comparable to that caused by a C(3)-ethoxycarbonyl group [12].



(1)

These significant results represent an important and useful umpolung [13] or reversal of reactivity at C(3) of bromopyrone 1a from an electrophilic center to a nucleophilic center, thereby allowing regiospecific attachment of a sulfur substituent as an electrophile. Indeed C(3) attachment of other electrophiles should be possible as well; we have had some initial success with introducing an allyl group.

We are actively studying the chemistry of 3-sulfinyl-2-pyrone (3) as well as the reactivity of the intermediate organocopper species (e.g. 5, 6) toward various electrophiles, and a full report will appear in due course.

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