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A Novel Approach to Tricyclic Pharmaceuticals via Directed Dilithiation of Diaryl Compounds[1]

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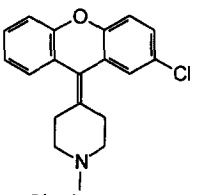
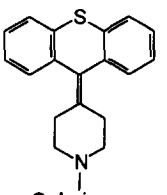
Abstract: Tricyclic compounds were prepared using a novel approach based on the reaction between dilithio-diphenyl ether with appropriately substituted esters. The pharmaceutical drug, clopipazan, and its corresponding deschloro analog were synthesized utilizing this approach. Copyright © 1996 Elsevier Science Ltd

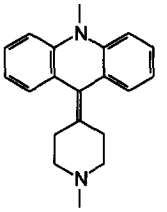
Tricyclic compounds such as clopipazan, chlorprothixene, calmixen, and its nitrogen analog exhibit various types of pharmacological activity.[2,3,4] These compounds usually contain a heteroatom in the central ring and an alkamine chain or a nitrogen-containing heterocycle attached to the carbon atom at the 9-position. This class of compounds form a significant part of one of the most extensive and well-studied group of drugs known as tricyclic pharmaceuticals and have found extensive use in treatment of various mental and physical disorders, such as psychosis, depression, epilepsy, Parkinson's disease, and various kinds of allergies.[2,3,4]

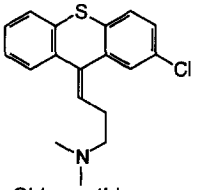


Clopipazan



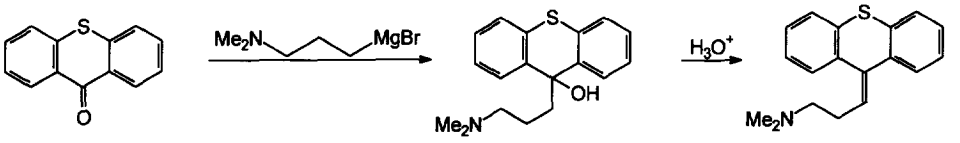
Calmixen





Chlorprothixene

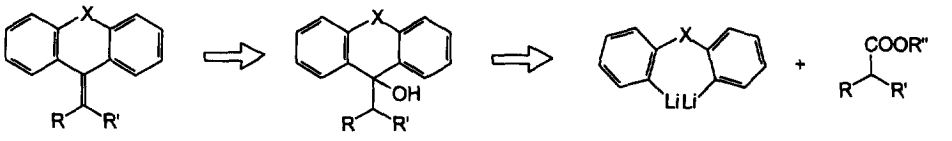
A frequently utilized approach[4] toward the syntheses of these compounds is the reaction between xanthone or thioxanthone and a Grignard reagent (Scheme 1) to yield the corresponding xanthenol. The xanthenol is subjected to acid-catalyzed dehydration conditions to obtain the desired tricyclic compound.



Scheme 1

We decided to examine an alternative approach toward the preparation of the tricyclic compounds based on the reaction of dilithio-diphenyl ether (or thioether) with appropriately substituted ester moieties. This approach is shown retrosynthetically in Scheme 2. Our approach would allow for the cyclization of the central ring and the introduction of the side chain in one step. Although this route may impose some limitations on

the nature of the substituents on the aryl moieties, it should also prove advantageous if the requisite ester is easier to obtain than the corresponding Grignard reagent.



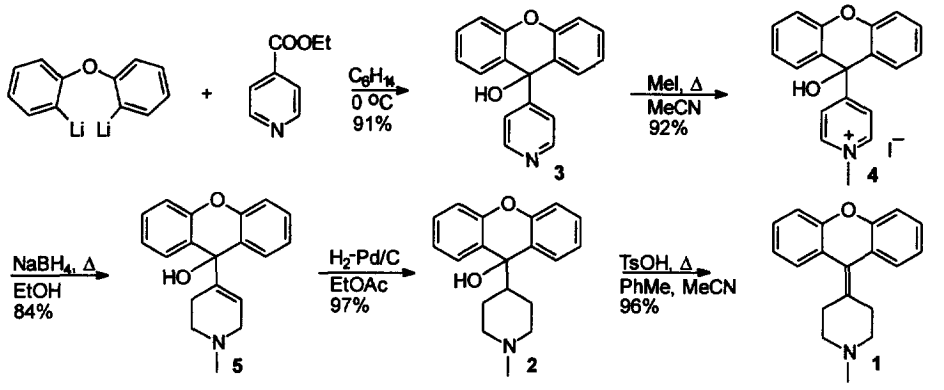
Scheme 2

The requisite *o,o'*-dilithiated species have been prepared previously[5] by halogen-metal exchange between butyllithium and *o,o'*-dibromo-diaryls. However, the preparation of the starting dibromides required several steps and led to modest overall yields.[5,6] Preparation of *o,o'*-dilithio-diphenyl ether by direct metallation of the commercially available Ph_2O in ethereal solvents[6] appears to be more convenient even though the yields are often low. Recently, a convenient lithiation procedure for Ph_2O and Ph_2S employing *n*-butyllithium in hexane in the presence of stoichometric amounts of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) has been reported.[7]

Preliminary studies[8] in our laboratories indicate that the lithiation of Ph_2O under the reported[7] conditions proceeds rapidly and with high regioselectivity. Thus, the reaction of Ph_2O with 2 equivalents of *n*-BuLi in hexane at room temperature in the presence of 2 equivalents of TMEDA gave mostly one dimethylated product. Upon quenching with excess MeI after 90 minutes, the reaction mixture reached the following composition (relative peak areas, monitored by GC-MS): 0.7% Ph_2O, 1.4% monomethyl-, 93.5% *o,o'*-dimethyl-, and 4.4% of its isomer. However, Ph_2S, reacted much more slowly when subjected to analogous reaction conditions and gave a mixture of several regioisomers of mono-, di-, and trimethylated diphenyl sulfides on quenching with excess MeI. This result is in accord with an earlier observation[9] that the lithiation of Ph_2S in ether gives a mixture of ortho and meta isomers of monomethyl-Ph_2S in a 9:1 ratio. This lack of regioselectivity is probably due to the weaker complexing strength of sulfur compared to oxygen.[10]

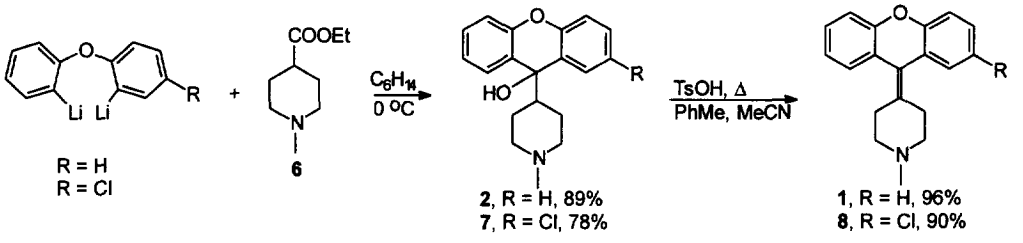
The deschloro analog **1** of clopipazan (**8**) was prepared in 96% yield by the acid-catalyzed dehydration of **2** using *p*-toluenesulfonic acid in refluxing toluene and acetonitrile. Xanthenol **2** was prepared via two different routes. In the first procedure (Scheme 3), ethyl isonicotinate was reacted with dilithio-diphenyl ether to give the expected **3** in 91% crude yield. It is important to point out that an easy two-step conversion of **3** into 11-(4-pyridyl)-dibenzo[b,f]-oxazepine, which has interesting pharmacological properties, has been reported previously.[11] However, the only synthesis of **3** found in the literature[11] involves the preparation of 4-pyridyllithium by metal-halogen exchange at -75 °C from the thermally unstable free base of 4-bromopyridine and leads to the final product in only 45% crude yield. Compound **3** was converted to the corresponding iodomethylate **4** in 92% yield by reaction with methyl iodide in refluxing acetonitrile. Upon refluxing with

$NaBH_4$ in absolute ethanol, **4** was reduced to **5** in 84% yield. The desired xanthenol **2** was obtained in 97% yield by the reduction of **5** with H_2-Pd/C in ethyl acetate as the solvent.



Scheme 3

Following another procedure (Scheme 4), **2** was prepared in 89% yield by the reaction between dilithio-diphenyl ether and **6**. The aminoester **6** was synthesized in 72% yield from ethyl isonipecotate using a modified version of the Eschweiler-Clarke methylation procedure.[12] A similar reaction between **6** and the *o,o'*-dilithiated derivative of 4-chlorophenyl phenyl ether afforded **7** in 78% yield. Xanthenol **7** was converted into the tricyclic pharmaceutical clopipazan **8** in 90% yield using the acid-catalyzed dehydration conditions mentioned above. High-field proton NMR and MS was used to determine the structures of all the products.



Scheme 4

Thus, tricyclic compounds based on the xanthenol skeleton can be prepared in good yields by reaction of dilithio-diphenyl ether with appropriate ester moieties. These tricyclic compounds can be converted into practical pharmaceutical drugs using simple dehydration reactions. Efforts are underway in our laboratories to prepare the more pharmacologically active sulfur and nitrogen analogs of xanthene.

Preparation of *o,o'*-dilithio-diphenyl ether: Diphenyl ether (1.7 g, 10 mmol) was placed in a dry 100 ml round bottom flask and was flushed with nitrogen. TMEDA (2.4 g, 20.7 mmol) was added via syringe followed by 10 ml of dry hexane and 13 ml of 15.1% *n*-BuLi in hexane (9.1 g, 21.5 mmol). The mixture was stirred at

room temperature for 90 minutes or longer before the addition of an electrophile.

Preparation of 9-(4-Pyridyl)-9-xanthenol (3): Dilithio-diphenyl ether (50 mmol) was prepared as described above in a 500 ml three-necked flask equipped with a mechanical stirrer and an addition funnel. The mixture was cooled in an ice-water bath, which led to precipitation of the TMEDA complex of *o,o'*-dilithio-diphenyl ether. Ethyl isonicotinate (7.6 g, 50.3 mmol) diluted to 50 ml with hexane was added dropwise over 10-15 minutes to the stirring suspension. The mixture was stirred for 1 hour at room temperature, then quenched by adding 50 ml of water and stirred for 30 minutes until the precipitate turned from greenish-gray to yellow. The hexane layer was decanted, the precipitate was suspended in water, filtered off, and washed with copious amounts of water on the filter until washings became colorless. The resulting pale-yellow product **3** was dried in a vacuum oven overnight and weighed 12.5 g (91% yield).

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