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Preliminary communication

Arylation of a carbanion derived from a pyridazine; a route to a functionalized arene

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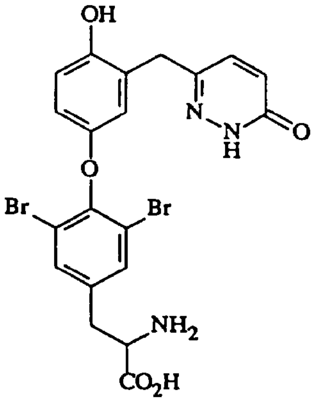
Abstract

1,4-Dichlorobenzene(cyclopentadienyl)iron(II) hexafluorophosphate reacts with the carbanion derived from 3-ethoxy-6-methylpyridazine N-oxide to give a Yanovsky-type adduct.

A recent report [1] on the reactions of aryloxy anions with organometallic aryl cation equivalents as a route to substituted diphenyl ethers prompts us to communicate our investigation aimed at the same target molecule. The hindered diphenyl ether SK & F L-94901 (**1**) is a selective thyromimetic which shows hypocholesterolaemic activity [2]. In contrast to the strategy employed by Hossner and



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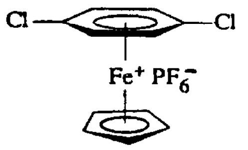

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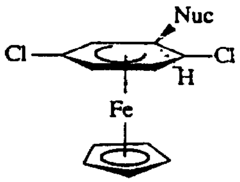

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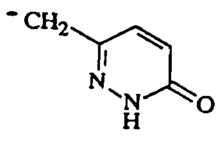

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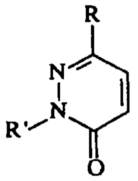
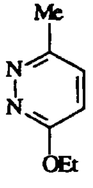
Voyle [1], who began their approach to this molecule with the construction of the diphenyl ether unit, we have chosen as the initial step the attachment of the heterocyclic moiety to a functionalized arene ring.

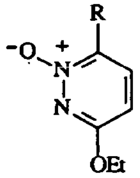
Our design is based upon the selective activation of 1,4-dichlorobenzene towards attachment of a nucleophile at either a substituted carbon or an unsubstituted carbon by complexation with the cyclopentadienyliron(II) unit. Soft carbanions, such as those generated from diethyl malonate or ethyl acetoacetate, are known to eventually displace chloride [3] from $(C_6H_5Cl)CpFe^+$, presumably via a series of reversible addition-elimination sequences. In contrast, Sutherland and co-workers have reported that hard carbanions, such as cyanide [4,5] or those derived from acetone [6] or butanone [7], attack a cationic iron complex carrying electron-withdrawing substituent(s) (e.g. **2**) *ortho* to an arene substituent to give a neutral cyclohexadienyliron(II) adduct (e.g. **3**). This transformation is analogous to the Yanovsky reaction [8] in which carbanions derived from ketones react with polynitroarenes leading to alkylation *ortho* to a nitro group. In the case of the Yanovsky-type reactions reported by Sutherland [5,6,7], the ketones were simple and readily available, and were used in excess together with KOH/H_2O at room temperature for 20 min. Our requirements, however, were more stringent since we needed to be able to generate and successfully add the carbanion **4**, or a synthetic equivalent of it, essentially in the stoichiometric ratio. To this end, 6-methylpyridazin-3-one (**5**) was prepared [9,10] and converted into its *N*-methyl derivative **6**. However, a series of experiments with a variety of bases (e.g. LDA, BuLi; followed by MeI) using a range of solvents and reaction temperatures indicated that deprotonation/trapping at the methyl group could not be achieved satisfactorily. Rather, nucleophilic addition to the heterocyclic ring by, for example, butyl carbanion, occurred. Consequently, **5** was converted into its *O*-ethyl aromatic derivative **7**



(**5**, R=Me, R'=H
6, R=Me, R'=Me)

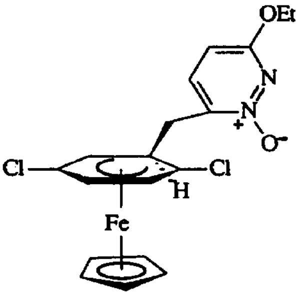


(**7**)



(**8**, R=Me
9, R=Et)

($2Ag_2O/EtI/MeOH$/room temperature/18 h; 60%) but trial experiments again showed that the derived primary carbanion could not be generated and trapped with MeI. However, formation of the N-oxide **8** ($3H_2O_2/HOAc$/90 °C/7.5 h; 66%) did provide a synthetic equivalent of **4**, which could be generated (BuLi/THF/ −100 °C/5 min) and then reacted with MeI (−78 °C/15 min, followed by warming to room temperature) to give the 6-ethyl homologue **9** in 83% yield. Moreover, addition of the solid cationic iron(II) complex **2** to the carbanion derived from **8** (−78 °C/15 min, then warmed to room temperature) afforded the desired *exo* Yanovsky-type adduct **10** in 63% yield (acceptable analytical and spectroscopic data have been obtained). Brief treatment of **10** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in acetonitrile at either room temperature or −23 °C gave the decomplexed



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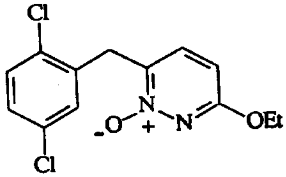

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functionalized arene **11** (43%), which carries chloro substituents appropriately placed for further conversion into SK & F L-94901 (**1**).

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