

Unusual $\text{KF}/\text{Al}_2\text{O}_3$ Promoted Tandem Electrophilic-Nucleophilic Aromatic Substitution Leading to the Xanthone Formation

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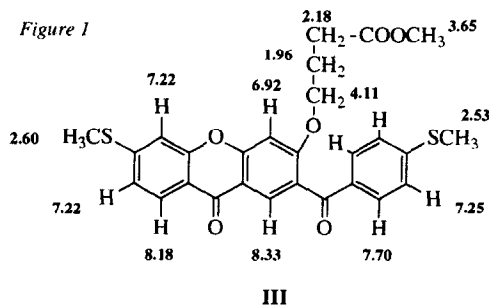
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Abstract: Formation of xanthone (III) by the $\text{KF}/\text{Al}_2\text{O}_3$ mediated O-alkylation of 2-hydroxybenzophenone (I) is described and mechanistic rationalization is proposed for this unexpected side-reaction.

The potassium fluoride on alumina continue to attract much interest from organic chemists due to the versatility of use in synthetic chemistry. This KF -alumina system has been used effectively in Michael additions, Knoevenagel condensations, C-, N-, O-, and S-alkylation reactions, aldol condensations, Wittig reaction, elimination reactions and has proved unique in syntheses of products not otherwise accessible.¹

In connection with our studies aimed at developing a safety-catch anchoring linkage (SCAL) for the synthesis of peptide C-terminal amides, we have faced the problem of alkylation of intramolecularly hydrogen bonded phenol (I).² We realized that fluoride ion activation could be the tool to overcome this obstacle since the fluoride ion is known to be a weakly basic, non-nucleophilic catalyst in many chemical processes involving hydrogen abstraction or hydrogen bond formation.³ Furthermore, in an effort to economize large scale preparation of SCAL linkage, highly priced $\text{Et}_4\text{N}^+\text{F}^-$ used in the original paper³ was replaced by much cheaper $\text{KF}/\text{Al}_2\text{O}_3$ reagent. Surprisingly, during the preparation of O-alkylated benzophenone (II) using this reagent, we isolated xanthone (III) which was formed as a by-product in 5-10% yield.⁴ So that alkylation of 2-hydroxy-4,4'-bis(methylthio)benzophenone (I) with methyl 4-bromobutyrate in the presence of $\text{KF}/\text{Al}_2\text{O}_3$ at room temperature for 48h afforded a mixture of O-alkylated benzophenone (II) and xanthone (III)⁵. The ratio of both products, however, depends upon the activity of $\text{KF}/\text{Al}_2\text{O}_3$ and was found to be variable between batches. The structure of (III) was determined by relay-COSY (H,H) NMR spectral measurement, data of which are given in Figure 1 (chemical shifts are in ppm). Proposed mechanism of the xanthone formation (Scheme 1) involves an initial

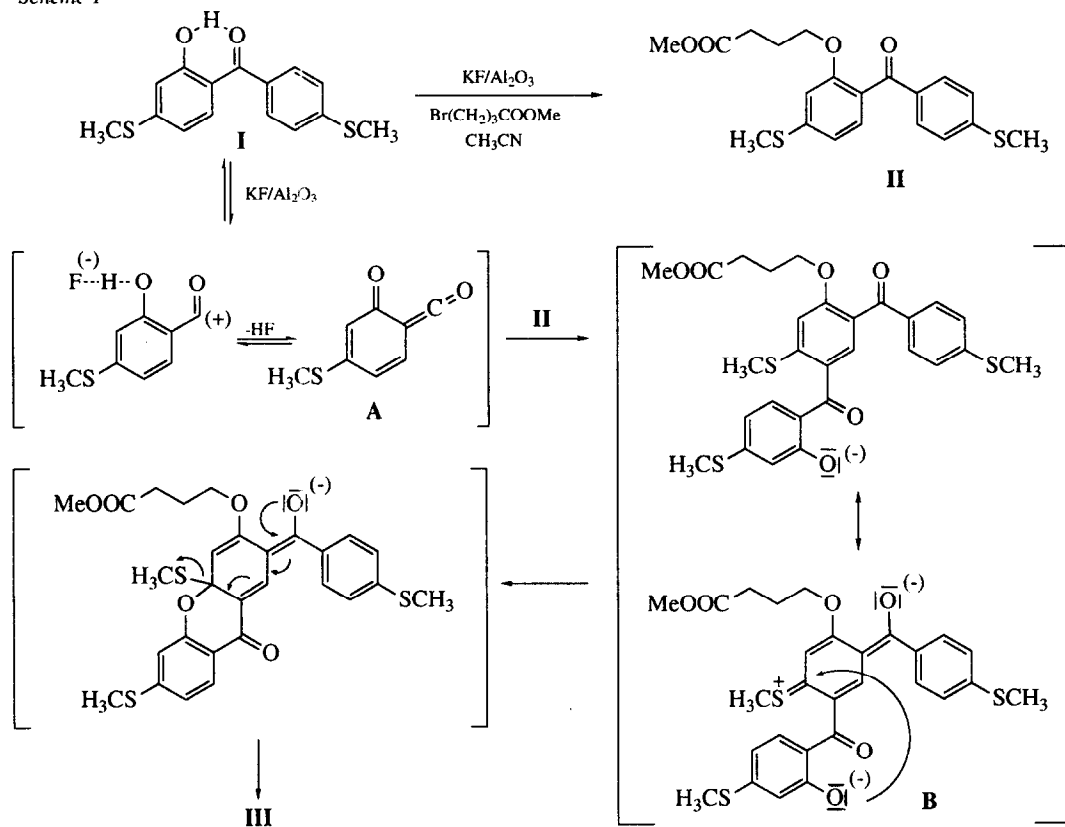
Figure 1



retro Friedel-Crafts reaction affording high reactive α -oxo-ketene (A) which acts as a strong electrophile in the following electrophilic aromatic substitution on the benzophenone (II). The consequent nucleophilic aromatic substitution involves an attack of phenolate anion at the dicoordinate alkylidenesulfonium ion (B) wherein methylthio group serves as a leaving group. The fluoride anion probably enhances the nucleophilicity of the phenol oxygen through strong F...HO hydrogen bonding.

In summary, although observed xanthone formation is of negligible general synthetic use yet, such a transformation appears to be new as does the product (III). Therefore, we conclude that the stage is now set to begin systematic investigations to make this synthesis much more practicable.

Scheme 1



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References and notes

1. L.M. Weinstock, J.M. Stevenson, S.A. Tomellini, S.H. Pan, T. Utne, R.B. Jobson, D.F. Reinhold, *Tetrahedron Lett.* 1986, **27**, 3845 and references cited therein.
2. M. Patek, M. Lebl, *Tetrahedron Lett.* 1991, **32**, 3891.
3. J.H. Clark, *Chem. Rev.* **80**, 429 (1980).
4. m.p. 137°C (EtOH); EI-MS: 508(M+,30), 421(30), 151(35), 101(100); UV(MeOH), λ_{max} (log ϵ): 216(4.5), 244(4.4), 266(4.3), 330(4.7).
5. A mixture of 30g of alumina (Fluka, Type 504C), 200ml of water and 20g of $\text{KF}\cdot 2\text{H}_2\text{O}$ was stirred for 30min. After evaporation of water under reduced pressure the modified alumina was dried at 130-140°C for 24h. A mixture of 1g of (I), 2g of the above prepared $\text{KF/Al}_2\text{O}_3$ in 10ml of CH_3CN was stirred at 20°C for 48h. After filtration and evaporation of solvent, the yellow oil was flash chromatographed (hexane:EtOAc, 60:40) to give the pure compounds (II) and (III).

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