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CARBON-CARBON CYANOETHYLATION OF ANISOLE AND ITS DERIVATIVES

Amareshwar Chatterjee and Braja Gopal Hazra,
Department of Chemistry, Jadavpur University,
Calcutta-32, India.

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In connection with the syntheses of polycyclic compounds related to steroid, we required an efficient direct method for introducing a three-carbon chain (e.g. $-CH_2.CH_2.CO_2H$) para to a methoxy group in an aromatic ring. The carbon-carbon cyanoethylation of the more active phenols, such as resorcinol, is known to give dihydrocoumarin derivatives in the presence of anhydrous zinc chloride and dry hydrogen chloride[1]. Simple phenol in the presence of more active catalyst, such as anhydrous aluminium chloride, affords β-(p-hydroxyphenyl)propionitrile[2] in good yield. Para-substituted phenols, under more drastic conditions, react with acrylonitrile to furnish dihydrocoumarin and its derivatives[3].

From the above facts, it seemed reasonable that anisole and its derivatives would behave like phenols in their reactions with acrylonitrile under acidic conditions. As far as we know, no such studies have been reported and this will be the subject matter of this communication.

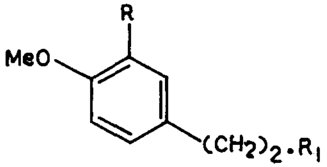
General procedure

Finely powdered anhydrous aluminium chloride (0.1 mole) was added slowly to a vigorously stirred cold solution of the methoxy compound (0.1 mole) and acrylonitrile (0.2 mole) in dry sym tetrachloroethane[4] (60 ml). Dry hydrogen chloride was then passed through the resulting mixture maintained at 10-15° for 1½ hr. The homogeneous reaction mixture was then heated in an oil bath maintained at 90-95° for 1½ hr with the continuous passing of dry hydrogen chloride. The dark red material was decomposed with cold water and the product was extracted with ether. The solvent after usual processing afforded the nitrile which was purified by vacuum distillation.

o-Cresyl methyl ether thus afforded the desired nitrile[5](I) (70%), b.p. 118°/0.2 mm (reported[6] b.p. 145°/8 mm); infrared (film), 2248 cm^{-1}($C\equiv N$); ultraviolet maximum, 276 mμ (log ϵ = 3.39). This nitrile was prepared before through a procedure[6] which involved several steps. Alkaline hydrolysis of the nitrile (I) furnished the known acid[6,7] (II) (77%), m.p. 99-100° (reported[6] m.p. 100°).

Simple anisole similarly yielded the unknown cyano compound(III) (60%), b.p. 127°/0.8 mm; infrared (film), 2246 cm^{-1} ($C\equiv N$); ultraviolet maximum, 277 mμ (log ϵ = 3.33). Hydrolysis of this nitrile gave the known acid (IV) (75%), m.p. 103-104° (lit.[8] m.p. 103.5-104°).

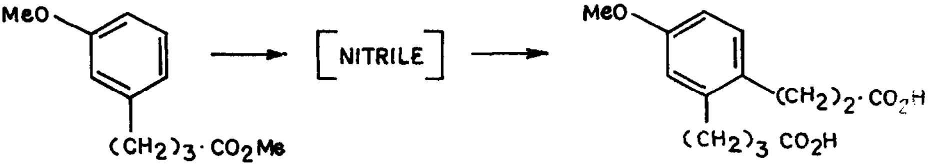
The present method is superior in its directness to the methods used previously for (II)[6,7] and (IV)[8].



I: R = Me ; R$_1$ = CN　　III : R = H ; R$_1$ = CN

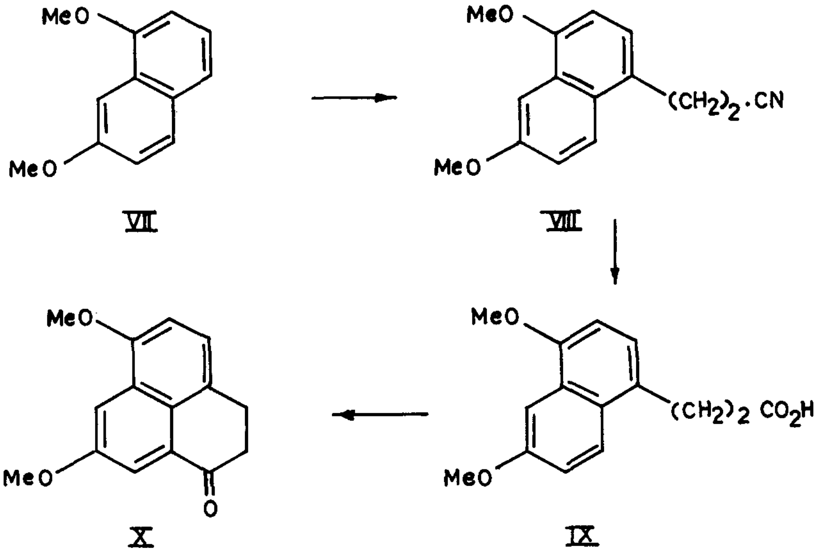
II : R = Me ; R$_1$ = CO_2H　　IV : R = H ; R$_1$ = CO_2H

Following the general procedure, methyl γ-(m-methoxyphenyl)butyrate(V)[9] furnished a small amount (12-13%) of a higher boiling nitrile which on usual hydrolysis afforded a dibasic acid, m.p. 123-124°; infrared ($CHCl_3$), 1708 cm^{-1} (carboxy C=O); ultraviolet maximum, 277 mμ (log ϵ = 3.20). This acid may tentatively be represented by the structure (VI).



V　　VI

1,7-Dimethoxynaphthalene (VII), under the general condition, afforded in low yield the crystalline nitrile(VIII) (18%) as needles, m.p. 104-105°; infrared ($CHCl_3$), 2248 cm^{-1} ($C\equiv N$); ultraviolet maxima, 248 (log ϵ = 4.50) and 285 mμ (log ϵ = 3.79. This nitrile was however isolated in 74% yield under controlled reaction conditions.[10] Compound (VIII) on alkaline hydrolysis furnished a crystalline acid (IX) (80%), m.p. 186-188°; infrared ($CHCl_3$), 1710 cm^{-1} (carboxy C=O); ultraviolet maxima, 250 (log ϵ = 4.46) and 285 mμ (log ϵ = 3.69). Polyphosphoric acid cyclisation of this acid yielded the ketone (X) (75%) as fine needles, m.p. 159-159.5°; infrared ($CHCl_3$), 1683 cm^{-1} (conjugated C=O in a six-membered ring); ultraviolet maxima, 266 (log ϵ = 4.66) and 318 mμ (log ϵ = 4.00). The formation of the ketone (X) thus unambiguously established the structures of the nitrile and the corresponding acid as (VIII) and (IX) respectively.



Presently, research is underway in order to expand the synthetic utility of the reaction.

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2. H. W. Johnston and F. J. Gross, J. Org. Chem., 22, 1264 (1957).
3. K. Sato, T. Amakasu and S. Abe, ibid., 29, 2971 (1964).
4. Of the few solvents tried, sym tetrachloroethane was found to be the suitable one especially to work with small quantity of methoxy compound.
5. All compounds described here gave expected elemental analyses. Ultraviolet spectra were taken in ethanol solution.
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9. The other products isolated were 6-methoxy-1-tetralone and some recovered starting material (V).
10. The reaction was performed at 5° for 3 hr and at 33° for ½ hr.