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THE ACTION OF SUBSTITUTED FORMAMIDES ON PHENYLFORMYLACETONITRILE—I

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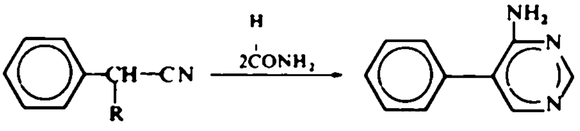
Abstract This paper describes the action of N,N-disubstituted formamides on phenylformylacetonitrile, leading to the formation of enamines. By a similar reaction, using secondary amines instead of formamides, a transformylation takes place.

BY REACTION between phenylacetonitrile and excess formamide, at 180°, 4-amino-5-phenylpyrimidine is obtained.[1] This reaction is completely general and has been extended to other arylacetonitriles.[2]

SCHEME 1



a, b

Ia R = H
b: R = CHO

Eiden and Nagar,[3] working with Ib and formamide, but using boiling amyl alcohol or benzene as solvents, obtained the enamine 1-cyano-1-phenyl-2-aminoethylene and the dienamine 1,5-dicyano-1,5-diphenyl-3-aza-1,4-pentadiene respectively.

According to these results, we tried the reaction between Ib and dimethylformamide, at 180°, and isolated a well crystallized compound, m.p. 79–80° Elemental analysis indicated the empirical formula $C_{11}H_{12}N_2$ and the mol wt determination (Rast) gave 182. The IR spectrum presents bands at 3077 (aromatic and olefinic), 2976, 2857 and 1377 (Me), 2198 (conjugated nitrile), 1631 and 1600 (conjugated ethylene and phenyl), 757 and 691 (monosubstituted benzene) and 836 cm^{-1} (trisubstituted C═C double bound). The UV spectrum, in ethanolic solution, presents absorption at 257 (ε, 10,210) and 295 nm (ε, 19,750).

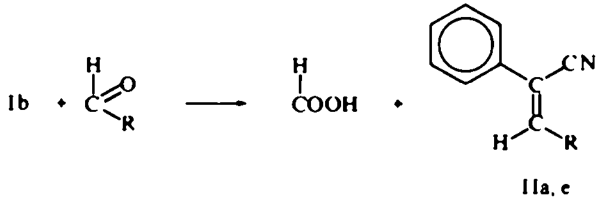
The NMR spectrum of the compound showed peaks at 7·28 (5H, aromatic), 6·9 (1H, vinyl) and 3·2 ppm (6H, N-dimethyl).

These data, together with its facile hydrolysis, regenerating the starting compound Ib, suggest an enamine of structure IIa.

The literature[4] gives δ 4·42–5·00 ppm for an enamine vinyl proton, differing from our findings, that are analogous to the value assigned for the vinyl protons of *trans*-stilbene.[5] This fact suggests for compound IIa a structure in which the phenyl and amino groups are *trans*. The high δ value obtained for the vinyl proton of IIa indicates strong long range deshielding produced by the Ph group.

The results obtained in the reaction of Ib with dimethylformamide encouraged us to try the action of other N,N-formylamines. The N,N-formyl derivatives used

SCHEME 2



IIa, e

IIa: R = dimethylamino
b: R = diethylamino
c: R = pyrrolidino
d. R = piperidino
e: R = morpholino

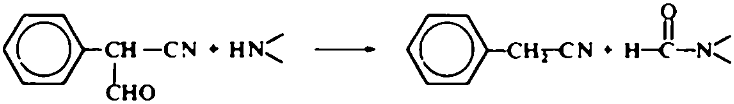
were those of diethylamine, pyrrolidine, piperidine and morpholine, and the desired enamine was isolated in each case; the IR UV and NMR data of these compounds were consistent with those of the parent compound IIa.

Using the experimental conditions given for disubstituted formamides, the reaction between Ib and N-monosubstituted formamides is more complex, and that will be the object of another publication.

Although enamines are easily alkylated or acylated, IIa did not react with methyl iodide or acetic anhydride, and in both cases it was recovered unchanged. This lack of reactivity is due to the proximity of the cyano group, that reduces the nucleophilicity of the vinylogous amino group.

In view of these results we tried to obtain IIe by the classical method of enamine preparation.[6] When morpholine was added to a benzene suspension of Ib, an exothermic reaction took place with complete solubilization of the formyl derivative. This solution was boiled under reflux for 6 hr and after distillation of the solvent and a liquid fraction, a variable amount of IIe remained in the flask. The liquid fraction proved to be a mixture of phenylacetonitrile and N-formyl morpholine, not separable by distillation because of the proximity of the b.ps. The separation was achieved by column chromatography on basic alumina, each component being identified by its IR spectrum, which was superimposable with that of an authentic sample.

SCHEME 3



Later experiments proved that heating was not necessary for this reaction, since if after mixing the reactants, the solution was allowed to reach room temperature and was then run through a basic alumina column, phenylacetonitrile and N-formyl morpholine were separated. By passing through basic alumina an ethereal solution of Ib, no phenylacetonitrile was detected, so transformylation did not occur during the separation. Analogously, the reaction between Ib and dimethylamine, diethylamine, pyrrolidine and piperidine was performed and in each case a mixture of phenylacetonitrile and the respective formamide was obtained. The reaction with diethylamine also afforded a small amount of IIb.

When more energetic conditions were used for the reactions (i.e. using *p*-toluenesulfonic acid as catalyst and toluene or xylene as solvent) besides the mixture of phenylacetonitrile and N,N-dialkylformamide, it was possible to isolate the enamine.

Several attempts were made to obtain enamines by heating phenylacetonitrile and N,N-dialkylformamides together, at 190° for several hours (with or without *p*-toluenesulfonic acid), but at the end of the heating period the reactants were recovered unchanged.

As the enamines obtained in these reactions are not formed by reaction of Ia and N,N-dialkylformamides, they should be produced by a classical enamine reaction or by a combination of the reactions depicted in schemes 3 and 2 (the N-formylamine formed in scheme 3 reacts with the unchanged formylphenylacetonitrile as in scheme 2) or by a combination of both.

Table 1 shows the amounts of morpholine enamine obtained using different reaction conditions and molar proportions of Ib and morpholine.

TABLE 1. REACTION BETWEEN Ib AND MORPHOLINE

I (mole)	Morpholine (mole)	Method	IIe (yield %)*
0·2	0·4	A	13·3
0·3	0·3	B	32·0
0·05	0·11	C	4·6
0·05	0·11	D	6·8
0·05	0·1	B	0
0·05	0·05	B	43·0
0·05	0·025	B	96·2

* based on morpholine.

Method A: with *p*-toluenesulfonic acid, xylene, OCa refluxing 16 hr in a soxhlet. *Method* B: without catalyst with benzene, refluxing 30 hr with Dean Stark trap. *Method* C: without solvent, no heating. *Method* D: without solvent, heating 8 hr at 160°.

These figures indicate that the enamine is formed by a combination of Schemes 3 and 2.

EXPERIMENTAL

All m.ps are uncorrected and were taken on a Fisher hot stage. IR spectra of solids were taken as KBr disks employing a Perkin–Elmer Model 21 spectrophotometer, and with neat samples of liquids on NaCl plates with a Perkin–Elmer Model 137B Infracord. Ultraviolet spectra were obtained with a Beckmann Model DU spectrophotometer using EtOH as solvent; the NMR spectra with a Varian A-60 spectrometer using CCl_4 as the solvent and TMS as an internal standard. The analysis were performed at this laboratory.

Phenylformylacetonitrile was obtained by reaction between ethyl formate and phenylacetonitrile,[7] dimethylformamide was a commercial product used without purification, N,N-diethylformamide was prepared according to the method of Bouveault,[8] and the rest of the N-formylamines were synthetized following the method of Auerbach for N-formylpiperidine.[9] The secondary amines were commercial products dried over solid KOH and distilled.

(1) *Reaction of* Ib *with* N,N-*disubstituted formamides*

A soln of Ib (14·5 g, 0·1 mole) in the appropriate disubstituted formamide (0·2–0·4 mole) was heated at 185° for 8 hr. If crystals separated after cooling, the reaction mixture was filtered and the solid washed in the filter with cold EtOH. If no crystals were formed, the reaction mixture was poured into water (100 ml) with stirring, and filtered after 1 hr, pressing the solid in the filter (rubber-dam). A few drops of phenylacetonitrile passed together with the water. The crystals were dissolved in benzene and precipitated with light petroleum ether and then recrystallized from EtOH.

During the heating period, a fair amount of liquid distilled. The distillate had a strongly acid reaction and proved to be an aqueous soln of formic acid.[10]

TABLE 2. REACTION OF Ib WITH N,N-DISUBSTITUTED FORMAMIDES

Enamine	Formula	m.p.	Yield %	Requires % C	Requires % H	Requires % N	Found % C	Found % H	Found % N
IIa	$C_{11}H_{12}N_2$	79–80	80·0	76·71	7·02	16·26	77·03	7·04	15·8
IIb	$C_{13}H_{16}N_2$	74 75	40·2	77·96	8·05	13·98	77·90	8·05	14·05
IIc	$C_{13}H_{14}N_2$	92–93	54·1	78·76	7·11	14·12	78·7	7·08	14·10
IId	$C_{14}H_{16}N_2$	99 99·5	50·0	79·20	7·59	13·19	79·2	7·23	13·15
IIe	$C_{13}H_{14}N_2O$	112–113	54·6	72·87	6·58	13·07	72·4	6·28	13·01

(2) *Reaction of* Ib *with secondary amines*

General procedure. The secondary amine (0·2–0·4 mole) was added slowly to a suspension of Ib (29 g. 0·2 mole) in anhyd benzene (40–50 ml). In the case of dimethylamine, the dry vapours were bubbled into the suspension. The resulting soln was heated under a Dean–Stark trap until no more water separated.

The solvent was removed *in vacuo*, and the oily residue was distilled at reduced press. The amount of distillate varied depending on the amine (dimethylamine 30·4 g; diethylamine 38·7 g; pyrrolidine 31·9 g; piperidine 36·8 g; morpholine 24·1 g). The components of the distillate were separated by chromatography on basic alumina. When the reaction was performed with morpholine, a small amount of enamine remained in the flask. Benzene extraction of the solid followed by precipitation with light petroleum ether, afforded IIe (8·7 g; 20·3 %).

Modification A. The general procedure was followed but toluene or xylene was used as solvent and *p*-toluenesulfonic acid (0·1–0·2 g) as catalyst. The residue in the distillation flask was taken with the minimum amount of benzene and the soluble enamine was precipitated with light pet. ether.

Modification B. The reaction was carried out as in modification A but passing the condensate through CaO in a Soxhlet.

Chromatographic separation of the liquid components of the above reaction. The distillate, diluted with ethyl ether was passed through a column of Merck basic alumina. The column was eluted with more ethyl ether until no more benzyl cyanide passed (checked by disappearance of the nitrile band). By elution with 98 % EtOH, the N,N-disubstituted formamide was obtained.

Concentration of the EtOH soln gave an oily residue, that was identified by its IR spectrum, superimposable with that of an authentic sample.

Acid hydrolysis of the enamines. The enamine (2 g) was dissolved in EtOH (10 ml), diluted with 100 ml of 10 % HCl aq and boiled under reflux until a clear soln was obtained. Upon cooling, Ib crystallized. It was obtained in yields of 87 to 94 % and identified by comparing its IR spectrum, m.p. and mixed m.p., with those of an authentic sample.

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