Tetrahedron. Vol. 28, pp 2377 to 2381. Pergamon Press 1972. Printed in Great Britain

THE ACTION OF SUBSTITUTED FORMAMIDES ON ARYLFORMYLACETONITRILES

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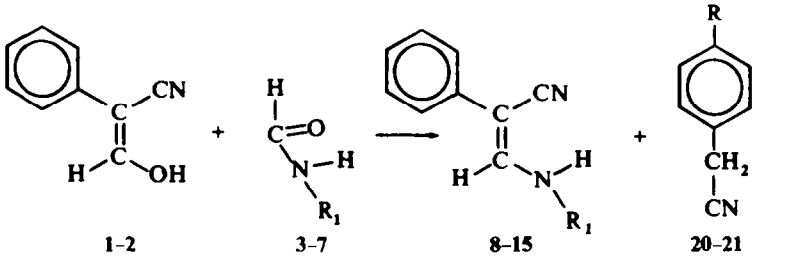
(*Received in the USA* 30 *August* 1971; *Received in the UK for publication* 18 *January* 1972)

Abstract—The reaction between phenyl- or *p*-methoxy phenylformylacetonitrile and monosubstituted formamides results in enaminonitriles. In some instances a simultaneous deformylation is observed. Formic acid is produced during the reaction and its origin was investigated.

PHENYLFORMYLACETONITRILE (**1**) reacts with formamide[1] or N,N-disubstituted formamides[2] giving enamines. To complete the study, the action of N-monosubstituted formamides on **1** was investigated.



1-2 R: **1** = H; **2** = OMe

3-7 R_1: **3** = Me; **4** = Et; **5** = $-CH_2$ phenyl; **6** = cyclohexyl; **7** = –phenyl

8-15 see table

20-21 R: **20** = H; **21** = OMe

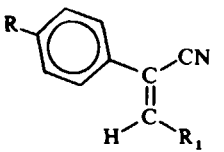
Compound **1** was heated at 160° with a fourfold excess of **3**, for several hours. The IR spectrum of product (**8**) showed bands at 3367 (NH), 2208 (conjugated nitrile), 1637 and 897 (trisubstituted C=C), 752 and 690 cm^{-1} (monosubstituted benzene).

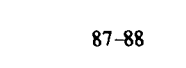
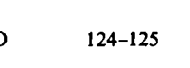
The NMR spectrum of **8** supported the enamine structure, giving peaks centered at δ: 3·07 (3H, d, J: 5 cps, N-Me), 7·03 (1H, vinyl) and 7·28 ppm (5H, m, aromatic): its UV spectrum, (EtOH) gave absorption at 213·1 (log ε: 3·53), 226·6 (log ε: 3·64), 239·1 (log ε: 3·32), 252·7 (log ε: 3·45), 265·2 (log ε: 3·35), 293·4 (log ε: 3·77), 301·7 (log ε: 3·71) and 314·1 nm (log ε: 3·74).

The synthesis was extended to *p*-methoxyphenylformylacetonitrile (**2**) and other mono- and disubstituted formamides, and in every instance the analytical and spectrophotometrical data of the products was consistent with those of the parent compounds.

However, besides the formation of enamines, the reaction also gave simultaneous deformylation of **1**. This secondary reaction took place only with aliphatic mono-

TABLE 1.



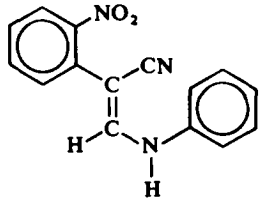
Enamine	R	R_1	M.p.	Yields%	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
8	H	—NH(Me)	99·5–100·5	38·0	75·92	6·37	17·70	76·01	6·42	17·60
9	H	—NH(Et)	53–54	51·0	76·74	6·97	16·27	76·89	7·03	16·20
10	H	—NH(Bz)	150–151	81·0	82·02	6·02	11·96	82·08	6·12	11·90
11	H	—NH(C_6H_{11})	126–127	72·1	79·60	8·01	12·39	79·67	8·09	12·28
12	H	—NH(Ph)	157·5–158·5*	81·6	81·81	5·45	12·72	81·92	5·47	12·68
13	—OMe	—NH(Et)	120–121	89·1	71·27	6·97	13·84	71·50	7·07	14·05
14	—OMe	—NH(C_6H_{11})	90–91	75·3	74·97	7·86	10·92	75·30	7·82	10·85
15	—OMe	—NH(Ph)	160–161	73·1	76·78	5·63	11·18	76·50	5·90	11·09
16	—OMe	—$N(Me)_2$	87·5–88·5	75·1	71·27	6·97	13·84	71·35	7·41	14·18
17	—OMe		87–88	70·4	74·39	7·49	11·55	74·50	7·40	11·75
18	—OMe		124–125	78·0	68·83	6·60	11·46	68·70	6·73	11·37
19	H	—$N(Ph)_2$	167·5–168·5	64·5	85·11	5·44	9·49	85·1	5·22	9·40

* Bibliog.[4] 157–158°

substituted formamides, with substantial lowering of enamine yields. The deformylation. reaction has been previously observed[2] when **1** was reacted with secondary aliphatic or alicyclic amines. These reactions were exothermic giving almost quantitative yields. The deformylation produced by the action of monosubstituted formamides required heating and the yields were temperature depended.

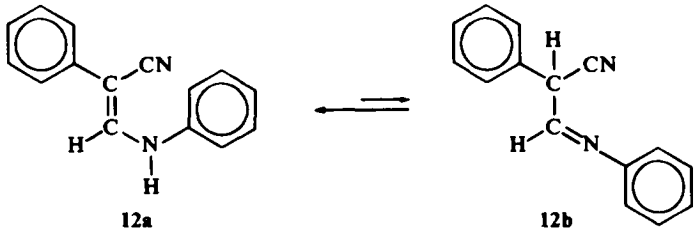
Thus, a good yield (51·0%) of **9** and consequently a low quantity of **20** was obtained with a bath temperature of 160°. Opposite yields were observed when reaction temperatures of 180–185° were used; under these conditions a lower quantity (26·6%) of **9**, together with a large increase (34·2%) of **20** was obtained. Similar results were observed for other reactions.

A recent paper[3] reported the isolation of *cis-trans* isomers of a N-monosubstituted enamine **22**, very similar to our compounds.



22

Since the synthesis of enamines **8-11** and **13–14** always gave one isomer, we prepared enamine **12** to see if the aromatic ring could influence the formation of geometrical isomers. Compound **12** was previously obtained by reaction between **1** and aniline,[4] giving only one isomer in equilibrium with the Schiff base.



12a **12b**

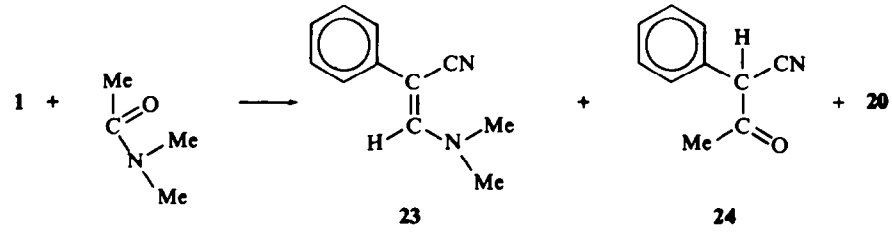
TLC determination of **12** gave one spot and the IR[4] and NMR[5] spectral data demonstrated an equilibrium between **12a** and **12b**, displaced towards the enaminic form. The predominance of **12a** over **12b** is in complete accord with the fact that **1** is almost completely enolized, as shown by its NMR spectrum.

Since the NMR determinations of **12** were always taken at the same temperature and the rotational energy barrier of enamines is low,[6] the existance of geometrical isomers at low temperatures is possible, but they were not isolated during work-up.

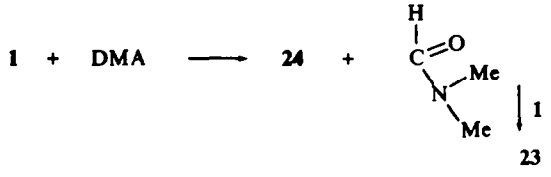
Splitting of the NMR signals for the N-Me moiety of **8** was assigned to the N–H proton, as was observed with N-methyl acetamide,[7] where the N-Me signal appears as a doublet (J: 4·7 Hz). This splitting was also observed with other N-monoalkylenamines.[5] By shaking a $CDCl_3$ solution of **8**, with D_2O the doublet was slowly

transformed into a singlet. H–D exchange was very slow and the doublet disappeared only after several hours.

In order to check the ability of other amides to be used as a source of enamines, the reaction between **1** and N,N-di-methylacetamide (DMA) was investigated. Examination of the products by TLC gave four spots, identified as unreacted **1** ($R_f = 0$), α-phenylacetoacetonitrile (**24**), enamine **23** and **20** by NMR, and IR comparison with authentic samples



The presence of both **24** and **20** in the reaction media accounts for the somewhat lower yield of **23**. As **24** does not react with DMF and since **1** is deformylated under the reaction conditions, it is possible that amide exchange did take place. The DMF so formed can react with **1** to give enamine **23**.



This scheme also explains why AcOH is produced in almost negligible amounts.

Lack of reactivity of **24** towards formamides was further verified when we tried to make it react with other formamides (aliphatic, alicyclic or aromatic), but **24** was always recovered unchanged.

EXPERIMENTAL

M.ps were made on a Thomas–Hoover Unimelt apparatus and are uncorrected. Yields of enamines refer to crude products. IR spectra were taken as Nujol mulls or neat liquids on NaCl plates with a Perkin–Elmer 137-E Infracord or KBr discs with a Beckman IR-20 apparatus. UV spectra were obtained with a Beckman DB-G spectrophotometer using EtOH as solvent. NMR spectra were run on a Varian T-60 or Perkin–Elmer R-12A instruments using CCl_4 or $CDCl_3$ as solvents and TMS as internal standard.

Phenylformylacetonitrile,[8] *p*-methoxyphenylformylacetonitrile,[9] and α-phenylacetoacetonitrile[10] were obtained by reaction of the appropriate arylacetonitrile with ethyl formate or acetate and EtONa.[10] DMF and diphenylformamide (commercial products) were used without further purification. The rest of the amides were synthetized by the method of Auerbach.[11] TLC and PLC separations were carried out on silica gel G (Merck) plates with F 254 indicator using $CHCl_3$ as eluant.

Synthesis of enamines. General procedure: a suspension of the nitrile (0·05 mole) in the appropriate formamide (0·1–0·2 mole) was heated at 140–160° until evolution of HCOOH ceased. If crystals separated after cooling, the mixture was filtered and solid washed with cold EtOH or benzene. If no crystals formed, excess amide was removed *in vacuo* and the residue dissolved in benzene and precipitated with light petroleum ether, then recrystallized from ligroine.

Enamines **8–9** were distilled at reduced pressure before recrystallization: their b.ps were 142–150°/1 mm and 170–172°/3 mm respectively.

Synthesis of **24**. A suspension of **1** (3·65 g; 0·025 mole) in DMA (8·7 g; 0·1 mole) was heated for 8 hr at 175°. Excess DMA was removed giving 6·02 g of dark oil which crystallized at 0°. TLC showed four spots at R_f: 0·0; 0·36; 0·6 and 0·8

An aliquot of the reaction products was dissolved in $CHCl_3$ and this solution was used for PLC. After elution, the components were visualized by short wave UV light and worked up as usual.

Band I: R_f: 0, unreacted phenylformylacetonitrile **1**.

Band II: R_f: 0·36, α-phenylacetoacetonitrile.

Band III: R_f: 0·6, enamine **23**.

Band IV: R_f: 0·8, benzyl cyanide **20**.

All compounds were identified by IR and NMR spectra and comparison with authentic samples by TLC.

Acknowledgements.—This work was supported by grants from the Consejo Nacional de Investigaciones Científicas y Técnicas and the Facultad de Farmacia y Bioquímica (U.B.A.). The authors are indebted to the Instituto Nacional de Farmacología y Bromatología for the T-60 NMR spectra. The R-12A spectrometer was purchased with a grant of the Fondo Especial para la Investigación Científica (U.B.A.).

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