REACTION OF o-ETHOXALYLAMINONITRILES WITH CYANOMETHYLENE COMPOUNDS IN THE PRESENCE OF CYANIDE ION

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Abstract When 2-ethoxalylaminonaphthalene-1-carbonitrile (I) was treated with potassium cyanide and some cyanomethylene compounds, such as ethyl and methyl cyanoacetates, α-cyanoacetamide and 1-cyanoacetylpyrrolidine, the corresponding 1-aminobenzo[f]quinazolines (IVa - IVd) were obtained.

Similarly, 6-ethoxalylaminoquinoline-5-carbonitrile (II) and 2-ethoxalylaminobenzonitrile (III) gave the corresponding 1-amino-2-pyrido[3,2-f]quinazolines (Va - Vd) and 4-aminoquinazolines (VIa - VIId), respectively.

The reaction of 2-nitronaphthalene with ethyl cyanoacetate and potassium cyanide in dimethylformamide (DMF) gives 2-ethoxalylaminonaphthalene-1-carbonitrile (I) and diethyl 2-cyano-3-(1-cyano-2-naphthylamino)fumarate. 6-Nitroquinoline reacts with ethyl cyanoacetate in a similar fashion to give 6-ethoxalylaminoquinoline-5-carbonitrile (II) and diethyl 2-cyano-3-(5-cyano-6-quinolylamino)fumarate.

Although the mechanism of the above reaction has not been established, concerning the formation of the fumarate derivative, we speculated that I or II initially produced from 2-nitronaphthalene or 6-nitroquinoline and ethyl cyanoacetate,
reacted with another molecule of ethyl cyanoacetate to form the fumarate derivative. However, it was found that the reaction of I with ethyl cyanoacetate in the presence of potassium cyanide did not give diethyl 2-cyano-3-(1-cyano-2-naphthyl-amino)fumarate but ethyl 1-amino-3-benzo[f]quinazolineacetate. We now wish to report the reactions of I, II and 2-ethoxalylaminobenzonitrile (III) with some cyanomethylene compounds.

Compound I was allowed to react with ethyl cyanoacetate and potassium cyanide in DMF at room temperature to form ethyl 1-amino-3-benzo[f]quinazolineacetate (IVa) in 43% yield together with recovery of I (22%). When the reaction was carried out at 70°, the yield of IVa increased to 63%. In a typical experiment, a solution of I (2 mmol), ethyl cyanoacetate (4 mmol) and potassium cyanide (4 mmol) in DMF (8 ml) was heated at 70° for 24 h with stirring. After removal of the DMF in vacuo, the residue was poured into ice water. The precipitate was collected, washed with water, dried and recrystallized from ethanol to yield IVa.

Similarly, the reaction of I with methyl cyanoacetate, α-cyanoacetamide and 1-cyanoacetylpyrrolidine gave the 1-amino-3-benzo[f]quinazolines (IVb, IVc and IVd) corresponding to IVa. Compound IVb was also obtained in 58% yield by reaction of 2-methoxalylaminonaphthalene-1-carbonitrile with methyl cyanoacetate. The results are summarized in Table.

Subsequently, compound II reacted with ethyl and methyl cyanoacetates, α-cyanoacetamide and 1-cyanoacetylpyrrolidine under the same conditions to give the corresponding 1-aminopyrido[3,2-f]quinazolines (Va, Vb, Vc and Vd). In a similar manner, compound III gave the corresponding 4-aminoquinazolines (VIa, VIb, VIC and VIId)(Table).

On the other hand, when 2-aminonaphthalene-1-carbonitrile, 2-acetamidonaphthalene-1-carbonitrile and 2-phenylmethanesulfonamidobenzonitrile were treated with ethyl cyanoacetate under the same conditions, no reactions occurred. The starting materials were recovered.

The formation of the aminoquinazolines can be explained by the scheme shown in the following Chart. Potassium cyanide seems to behave as a base. Cyanide ion abstracts a proton from the ethoxalylamino group in α-ethoxalylaminobenzonitriles (I - III) to form the amide ions, which add to the nitrile carbon of cyanomethylene compound to form amidines as an intermediate, which cyclize to give amino-quinazolines (IV - VI) with elimination of the ethoxalyl group.
Both IVa and IVb were hydrolyzed by heating them with 10% hydrochloric acid to provide the same compound, 3-methylbenzo[f]quinazolin-1(2H)-one. On hydrolysis with 10% hydrochloric acid, Va gave 3-methylpyrido[3,2-f]quinazolin-1(2H)-one, which was identical with an authentic sample prepared from 6-acetamidoquinoline-5-carbonitrile by the method of Bretschneider et al. Similarly, compound VIa gave 2-methyl-4(3H)quinazolone. The structure assignment of IV, V and VI was based on the data of hydrolysis, the satisfactory elemental analyses and the spectral data.
Table Reaction of o-Ethoxalylaminonitriles with Some Cyanomethylene Compounds\textsuperscript{a)}

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\begin{align*}
\text{CN} & \quad \text{HN} \quad \text{CO} \quad \text{OC}_{2}\text{H}_5 \\
\text{CN} & \quad \text{CH}_2 \quad \text{R} , \quad \text{KCN}
\end{align*}
\]

| Substrate | R | Product\textsuperscript{b)} | Yield\textsuperscript{c)} (%) | mp\textsuperscript{(°C)} (| Recrystn. solvent) | Appearance |
|-----------|---|------------------|-----------------|-----------------|-------------|
| I         | a: R=-COOC\textsubscript{2}H\textsubscript{5} | IV\textsubscript{a} | 63 | 185 - 186 (EtOH) | Colorless needles |
|           | b: R=-COOCH\textsubscript{3} | IV\textsubscript{b} | 59 | 164 - 165 (MeOH) | Colorless plates |
|           | c: R=-CONH\textsubscript{2} | IV\textsubscript{c} | 76 | 258(dec.) (MeOH) | Colorless needles |
|           | d: R=-CO-N & H \textsuperscript{c} | IV\textsubscript{d} | 57 | 215.5 - 216.5 (MeOH) | Pale yellow needles |
| II        | a  | Va | 57 | 200 - 201 (EtOH) | Colorless needles |
|           | b  | Vb | 43 | 220.5 - 221(dec.) (MeOH) | Colorless columns |
|           | c  | Vc | 60 | 271 - 272.5(dec.) (MeOH) | Colorless needles |
|           | d  | Vd | 64 | 282 - 284 (MeOH) | Yellow needles |
| III       | a  | VI\textsubscript{a} | 41 | 174.5 (Acetone-ether) | Colorless needles |
|           | b  | VI\textsubscript{b} | 49 | 202 - 203 (MeOH-ether) | Colorless needles |
|           | c  | VI\textsubscript{c} | 46 | 261 - 263(dec.) (MeOH) | Colorless needles |
|           | d  | VI\textsubscript{d} | 45 | 218 - 219 (MeOH-ether) | Colorless needles |

\textsuperscript{a)} All reactions were carried out in DMF for 24 h at 70°C.
\textsuperscript{b)} All products gave the expected microanalytical and spectral data.
\textsuperscript{c)} Yield of purified product.
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REFERENCES AND NOTE
3. IVa. IR (KBr) cm$^{-1}$: 3415, 3300 (NH$_2$), 1715 (CO). $^1$H-NMR (DMSO-d$_6$) $\delta$: 1.19 (3H, t, $J$=7.5 Hz, -OCH$_2$Cl), 3.80 (2H, s, -CH$_2$-), 4.13 (2H, q, $J$=7.5 Hz, -OCH$_2$CH$_3$), 7.36 (2H, br.s, -NH$_2$), 7.56 (1H, d, $J$=9 Hz, C$_5$-H), 7.58-8.10 (3H, m, C$_7$-9-H), 8.11 (1H, d, $J$=9 Hz, C$_6$-H), 8.76 (1H, m, C$_{10}$-H).
   MS m/e: 281 (M$^+$).

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