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N-ALKYLATION OF NITRILES—III

HETEROCYCLIZATIONS BY AMINOLYSIS OF NITRILIUM SALTS: IMIDAZOLES, 4-OXOQUINAZOLINES AND 4-QUINOLONES[1]

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Abstract—Several heterocyclizations have been carried out by aminolysis of nitrilium salts with aminoesters or propargyl amine. The aminolysis with norvaline methyl ester gave a 5-hydroxyimidazole derivative **8**. With a β-aminoester such as methyl anthranilate, the amidinoesters **10** first obtained cyclized to 4-oxo-quinazolines **11**. With a N-t-butyl substituted amidine ester **13**, the ring closure occurred on the carbon α to the amidine giving a 2-amino-4-quinolone **14**. It is only by refluxing in a strong base such as potassium t-butanolate in t-butunol that the oxoquinazoline **15** is obtained. Another type of ring closure occurred when the nitrilium salt was treated with propargylamine: the propargylamidine **16** formed was converted during the working up in the imidazole derivative **17**.

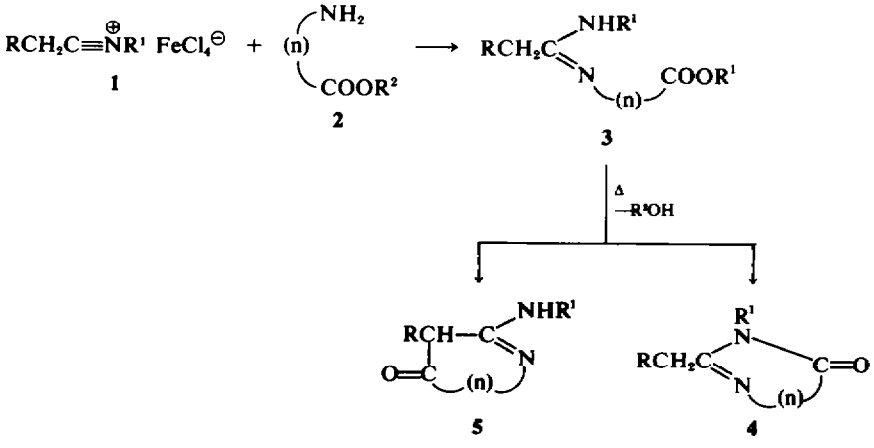
Nitrilium salts are useful in a large number of heterocyclizations.[2] As an extension of our study on the N-alkylation of nitriles[1,3] we report on several which have not been described before.

The aminolysis of the nitrilium salts produce N-substituted amidines.[1,3] When this reaction is carried out with an aminoester **2** the amidine-ester **3** formed can cyclize in different ways depending on the starting material and the experimental conditions. An intramolecular cyclisation is usually observed at the remaining NH of the amidine and the elimination of alcohol thus leading to an heterocycle such as **4** (or a tautomeric form). When R^1 is a t-Bu group the ring closure takes place on the carbon adjacent to the amidine group giving **5** (or a tautomeric form; see details below).

Aminolysis with α-aminoesters. The aminolysis of N-isopropylacetonitrilium tetrachloroferrate (**6**) obtained as described previously[3] treated with norvaline methyl ester gave on distillation a 40% yield of the 5-hydroxy-imidazole derivative **8** via the amidine ester **7**. The NMR spectrum of **8** indicates the presence of two tautomeric forms (Experimental).

Aminolysis with β-aminoesters. According to the general equation, the aminolysis of the nitrilium salt with a β-aminoester such as methylanthranilate gives 3,4-dihydro-4-oxo-quinazolines (**11**) in 60–70% overall yield (based on the starting nitrile).

The amidinoester **10** is usually not isolated because the ring closure takes place at room temperature. Heating under reflux in a solvent or better in alcoholate-alcohol, completes the reaction. The



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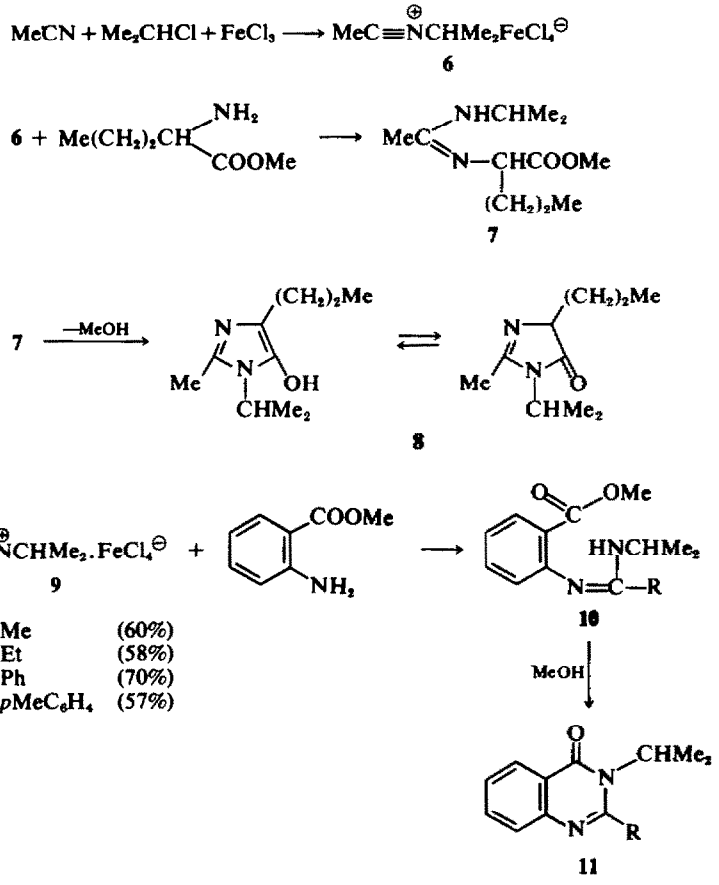


NMR spectrum of the amidine **10c** could, however, be recorded and revealed a 30% transformation to **11c** after 3 days on standing at room temperature. The physical and spectral data are given in Tables 1, 2, and 3 and are in agreement with the proposed quinazolone structure **11**.[5] One of them **11a** has been described recently in the literature.[6]

The amidinoester **13** prepared from N-t-butyl-acetonitrilium tetrachloroferrat and methyl anthranilate in 50% yield is very stable. It can be distilled in vacuum without change at 120°. Interestingly when **13** is heated 6 hr under reflux in *o*-dichlorobenzene a ring closure takes place, giving the 2-amino-4-quinolone **14** derivative in 80% yield. Related intramolecular C-acylations have been encountered before.[4] Heating the amidinoester **13** in a strongly basic medium such as sodium methanolate in methanol or potassion t-butylate in t-butanol yields the quinazolone derivative **15**. This shows the delicate balance between the nucleophilicity and the steric hindrance for the amidine cyclisation. The structures are based on the physi-

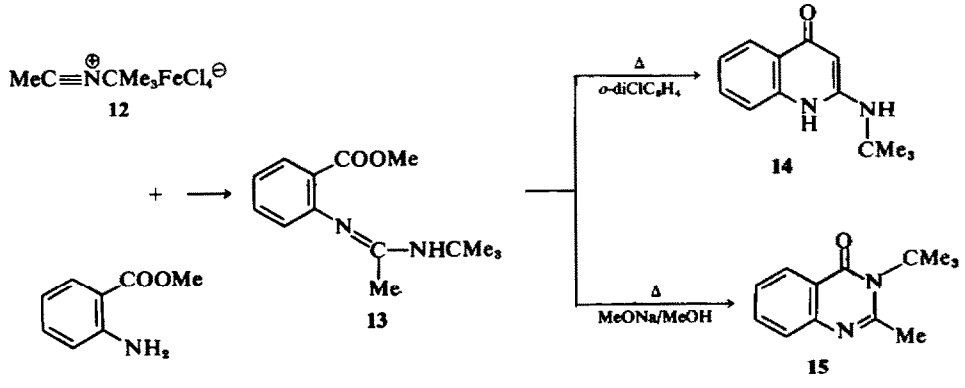


Table 1. Physical and elementary analyses of the 2,3-disubstituted-3,4-dihydro-4-oxoquinazolines **11** and **15**

No.	m.p. °C or b.p.	Solvent of cryst.	Formula	MW	Calc. C	Calc. H	Calc. N	Calc. O	Found C	Found H	Found N	Found O
11a	88–91	ether–light petroleum	$C_{12}H_{14}N_2O$	202	71·3	6·94	13·85	7·93	71·34	7·13	13·80	8·17
11b	56–60	light petroleum 40–60	$C_{13}H_{16}N_2O$	216	72·19	7 46	12·95	7·40	72·36	7·42	12·94	7·34
11c	138–140	benzene–light petroleum	$C_{17}H_{16}N_2O$	264	77·25	6·10	10·60	6·05	77·28	6·17	10·61	6·27
11d	134–140	benzene–light petroleum	$C_{18}H_{18}N_2O$	278	77·67	6 52	10·07	5·75	77·52	6·50	10·15	5·80
15	110–120°/0·1	pentane	$C_{13}H_{16}N_2O$	216	72·19	7·46	12·95	7·40	71·91	7·48	12·78	7·97

Table 2. IR and UV spectra of the 2,3-disubstituted 3,4-dihydro-4-oxaquinazolines **11** and **15**

No.	IR (μ)	UV λ_{max}^{mu} ($\epsilon \cdot 10^{-3}$) methanol
11a	6·0; 6·2; 6·3; 6·35	317 (2·7); 305 (3·5); 267 (8·4); 226 (26·5); 207 (30·0); CH_3OH
11b	6·0; 6·2; 6·3; 6·4	318 (2·4); 305 (3·2); 265 (8·1); 225 (24·5); 206 (28·6); CH_3OH
11c	6·0; 6·25 6·3; 6·35	315* (4·0); 305* (5·2); 278 (10·8); 228 (29·2); 205 (52·4)
11d	6·0; 6·25; 6·3; 6·4	315* (3·9); 305* (5·7); 279 (10·9); 230 (28·0); 206 (41·7)
15	6·0; 6·2; 6·3; 6·4	310 (3·0); 274(6·5); 228 (25·2); 206 (23·5)

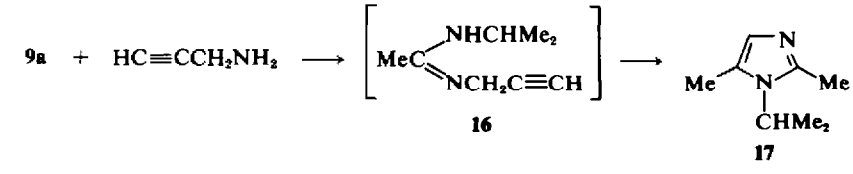
*shoulder.

Table 3. NMR spectra of the 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines **11** and **15**

No.	Solvent	τ [relative intensity] multiplicity
11a	CCl_4	1·92 [1] m; 2·4–2·8 [3] m; 5·47 [1] sept; 7·45 [3] s; 8·39 [6] d
11b	CCl_4	1·90 [1] m; 2·4–2·9 [3] m; 5·50 [1] sept; 7·21 [2] quart; 8·38 [6] d; 8·66 [3] trip
11c	$CDCl_3$	1·72 [1] m; 2·2–2·7 [3] m; 2·45 [5] s; 5·65 [1] sept; 8·40 [6]
11d	$CDCl_3$	1·73 [1] m; 2·2–2·8 [7] m; 5·60 [1] s; 7·57 [3] s; 8·40 [6] d
15	$CDCl_3$	1·95 [1] m; 2·3–2·9 [3] m; 7·30 [3] s; 8·23 [9] s

cal and spectral data (see Tables 1, 2, and 3 and Experimental).

Aminolysis with propargylamine. Another type of ring closure is via the aminolysis of the nitrilium salt **12** with propargylamine. The acetylenic amidine **16** first formed could not be isolated and the imidazole derivative **17** was obtained in 40% yield. Related ring closures have been recently reviewed.[7]



EXPERIMENTAL

Technical assistance of Mrs. E. Szalai.

M.ps and b.ps are uncorrected. IR spectra were taken as KBr pellets with a Perkin-Elmer model 21, double-beam instrument, UV spectra with a Cary recording spectrophotometer model 14 and NMR spectra on a Varian A 60 instrument, using TMS as internal standard. The NMR spectra have been recorded and interpreted by Mr. R. Merényi.

5-Hydroxy-4-propyl-1-isopropyl-2-methyl-imidazole **8**. The N-isopropyl acetonitrilium tetrachloroferrat **6** was prepared from $FeCl_3$ (9 g; 0·055 M), MeCN (2·28 g; 0·0555 M) in 50 ml i-PrCl as in the preceding paper.[3] Crude **6** was taken up in 30 ml CH_2Cl_2 and to this stirred suspension cooled at −10° norvaline methyl ester (6·9 g) was added dropwise. The mixture was kept overnight at room temp and the solvent evaporated to dryness. NaOH (12 g; 0·3 M) as a 30% soln was added to the residue with stirring, the mixture extracted with ether and dried leaving a residue (6 g) which was distilled at 82°/0·1 mm Hg, yielding 3·6 g of the liquid **8** (40%); NMR (CCl_4): τ [H] m: 6·03 [1] 7; 6·3 [1] m; 7·84 [1·7] s; 7·88 [1·3] s; 8·4 m; 8·62 d; 8·64 d; 8·6 m; 9·05 m; from 8·62 to 9·05 the relative intensities correspond to 13 protons. The rela-

tive intensities of the signals at 7·84 and 7·88 corresponding together to the Me in position 2 of the imidazole derivative **8** represent a relative tautomeric ratio of 57/43.

Amidinoesters **10** *and ring closure to* 3,4-*dihydro*-4-*oxoquinazolines* **11**. The nitrilium salt **9** was prepared from the corresponding nitrile, $FeCl_3$ in i-PrCl as solvent by the methods described.[3] The crude **9** was taken up in CH_2Cl_2. Methylanthranilate was added to this stirred and ice-cooled mixture which was then kept overnight at room temp. The CH_2Cl_2 was evaporated to dryness and an excess of 30% NaOH/H_2O was added to the residue. It was then extracted with ether, dried and the ether evaporated leaving a residue of **11**. Starting from benzonitrile, this residue, however, was the amidine ester **10c**; IR (KBr) 5·8 s; 6·15 s; 6·3 m; 6·4 m; 8·12 s; UV (MeOH) $\lambda_{max}^{mμ}$ (ϵ): 227 (26·600); 278 (9·100); NMR (CCl_4): 2·2–3·6 [10] m; 5·6 [1]; 6·23 [3] s; 8·68 [3] dd. (Found: C, 73·43; H, 6·51; N, 9·57; O, 10·44; Calc. for $C_{18}N_{20}N_2O_2$: C, 72·95; H, 6·80; N, 9·45; O, 10·80%; MW 296). The compound was cyclised on standing for a few days or better by heating under refluxing for 2 hr with 2N MeONa in MeOH. Then the MeOH was evaporated to dryness, the residue taken up in CH_2Cl_2, washed with water, the soln dried over Na_2SO_4 and concentrated. The residue (**11c**) crystallized from benzene-light petroleum. The preparation of **11d** was similar to that of **11c**.

Amidinoester **13**. The synthesis of **12** and its aminolysis with methyl anthranilate was carried out as described.[3] The crude **13** was extracted with ether, dried then concentrated; the oily residue was distilled from a 3-bulb tube collecting the fraction b.p. 100–120°/0·1 mm Hg. This was crystallized from pentane, m.p. 54–55°; yield 50%. (Found: C, 67·90; H, 8·16; N, 11·15; O, 12·92; Calc. for $C_{11}H_{20}N_2O_2$: C, 67·71; H, 8·12; N, 11·28; O, 12·89%): IR (μ): 5·80 s br; 6·05 s br; 6·22 s. UV (MeOH) $\lambda_{max}^{mμ}$ (ϵ): 308 (3700); 215 (28200); NMR (CCl_4): 2·37 [1] m; 2·82 [1] m; 3·22 [1] m; 3·50 [1] m; 5·9 [1] enlarged; 6·28 [3] s; 8·40 [3] s; 8·63 [9] s.

2-*Methyl*-3-t-*butyl*-3,4-*dihydro*-4-*oxoquinazoline* **15**. The amidine **13** (1 g) in 10 ml MeOH and 2 ml NaOMe in MeOH (2N) was heated under reflux for 16hr. The MeOH was evaporated to dryness, the residue taken up in chloroform, the organic soln washed with water, dried and concentrated. The crude product was distilled from a 3-bulb tube at 120–130°/0·5 mm Hg. The NMR of the distillate showed it to contain 60% of **15** and 40% of the starting amidine **13**. The amidine **13** (5 g) in 4 g t-butanolate and 10 ml t-butanol was heated 2 hr under reflux. The same working up furnished a distillate which crystallized from pentane, yield 2 g (50% of pure quinazoline **15** (Tables 1, 2 and 3).

2-t-*Butylamino*-4-*quinolone* **14**. The amidine **13** (4 g) in 8 ml *o*-dichlorobenzene was heated under reflux for 3 hr, the first crystals appeared while the soln was boiling. The cooled soln was filtered giving 1·6 g of **14**. The filtrate was refluxed for another 3 hr and the cooled filtered soln furnished another 1·2 g. The two fractions were crystallized together from MeOH, yield 80%; m.p. > 260°. (Found: C, 72·19; H, 7·28; N, 12·96; O, 7·85;Calc. for $C_{13}H_{18}N_2O$: C, 72·19; H, 7·46; N, 12·95; O, 7·40%; MW 216); IR (KBr) μ: 6·05 s; 6·25 s; 6·55 s; 6·7 s; 6·87 s; UV (MeOH) $\lambda_{max}^{mμ}$ (ϵ): 300 (16800); 245 (33200); 235 (33400); 225 (34000); NMR (DMF at 80°): 2·05 [1] m; 2·6–3·1 [~ 3] m; 4·25 [1] s; 8·57 [9] s; 2 protons are exchanged in CF_3COOD.

2,4-*Dimethyl*-3-*isopropylimidazole* **17**. The salt **9a** was prepared from MeCN (3·16 g) and $FeCl_3$ (12·5 g) in 50 ml i-PrCl. To the crude p.oduct in 40 ml of CH_2Cl_2 was added dropwise under stirring and ice-cooling, propargylamine (5 g) in 10 ml CH_2Cl_2. The mixture was kept overnight in the refrigerator, it was then hydrolysed with a 30% NaOH aq and the mixture extracted with ether. The organic layer was dried, concentrated then distilled. The fraction collected at 60°/0·5 mm Hg was pure **17**; yield: 40%. (Found: C, 69·63; H, 10·09; N, 19·78; Calc for $C_8H_{14}N_2$: C, 69·52; H, 10·21; N, 20·27%; MW 138); UV (MeOH) 215 μ (6200); NMR (CCl_4): 3·68 [1] enlarged; 5·66 [1] sept; 7·72 [3] s; 7·8 [3] s; 8·56 [6] d.

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