A NEW ACCESS TO 2-BENZOYLQUINOLINE AND 1-BENZOYLISOQUINOLINE USING A NOVEL MODE OF BASE-INDUCED DECOMPOSITION OF N-ALKOXYPYRIDINIUM SALTS

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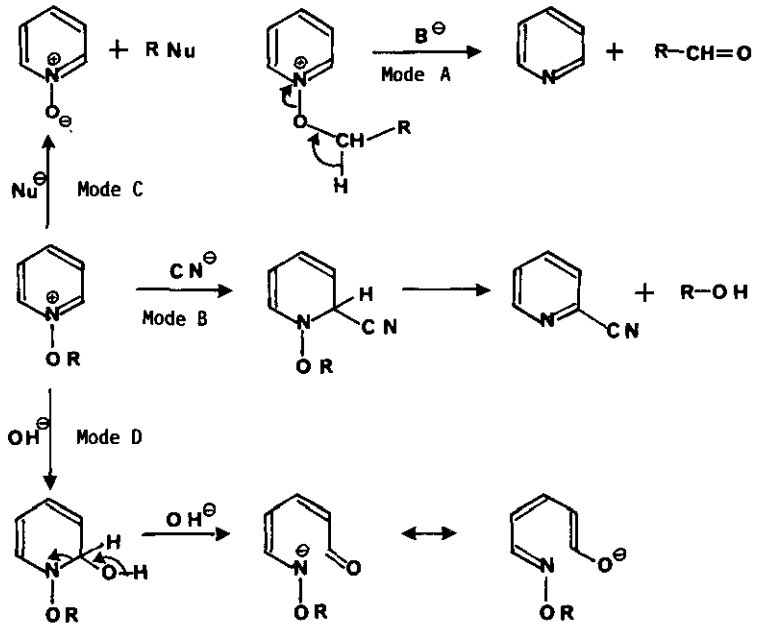
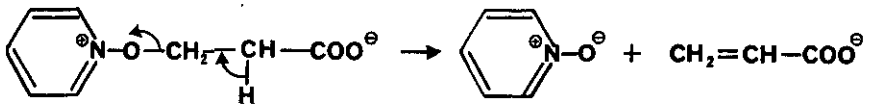
Abstract - A novel mode of fragmentation alkoxylogous of Katritzky's mode A of decomposition of N-alkoxypyridinium salts can become exclusive in the quinoline and isoquinoline series, providing a new access to benzoyl derivatives of these heterocycles.

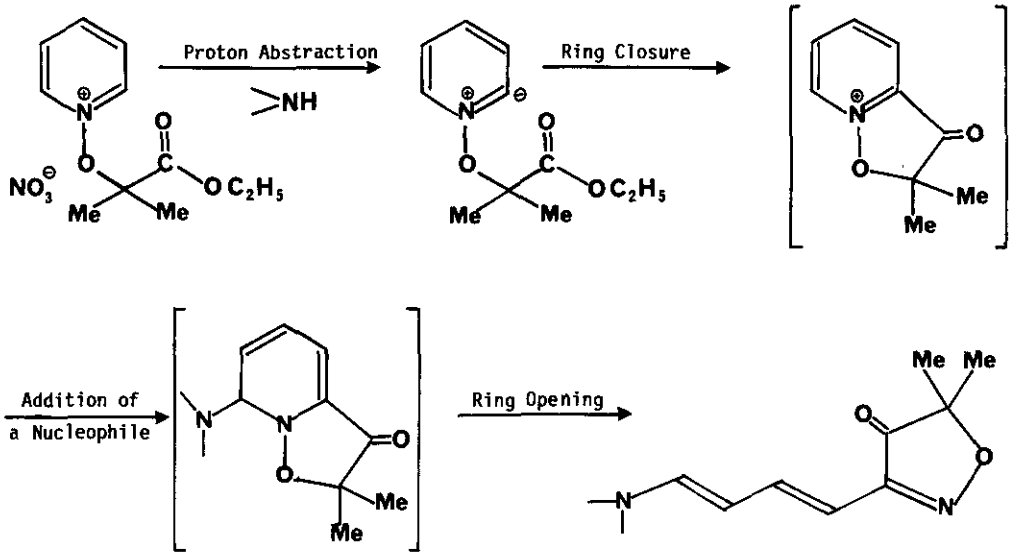
In addition to the four classical modes of reaction of N-alkoxypyridinium salts with nucleophiles depicted by Katritzky[2-4] in the following scheme, our previous studies[5,6] of such salts bearing a functional group in their alkoxyl chain had put in evidence some new modes of base-induced decomposition of these versatile coumpounds.



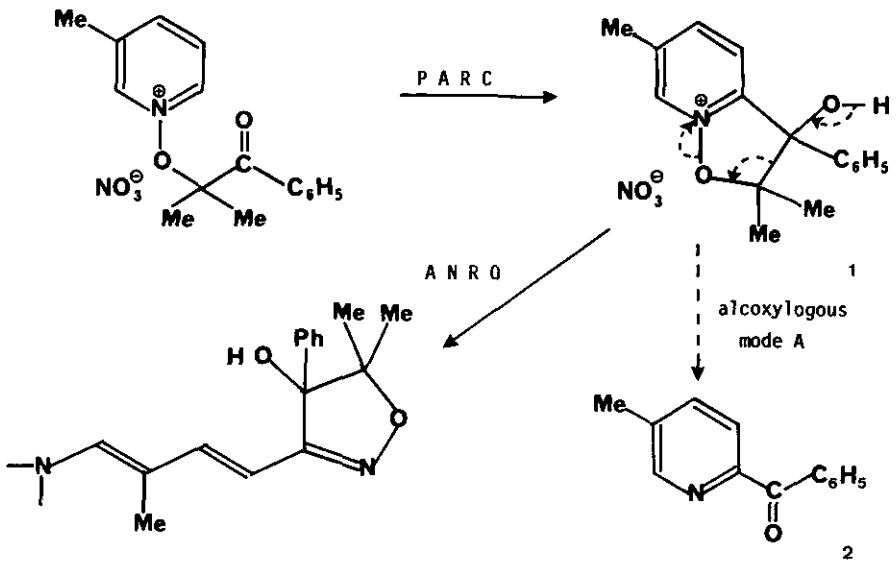
In this field we have shown that a β-elimination, in which the heterocyclic N-oxide acts as a leaving group can compete with the classical decomposition to pyridine and a carbonyl derivative according to path A[6,7].



Furthermore the presence of a suitable functional group (as ketone or ester) in the alkoxyl chain enables an intramolecular cyclization to take place. This one occurs by condensation of the functional group with an ylid which is first formed by base-promoted deprotonation of the salt in position-2 or -6[8]. A subsequent ring opening according to path D leads to isoxazoline derivatives[6]. The overall process affords a new heterocyclic ring conversion for which we have proposed the PARC-ANRO[10] mechanistic sequence described in the following scheme[11].



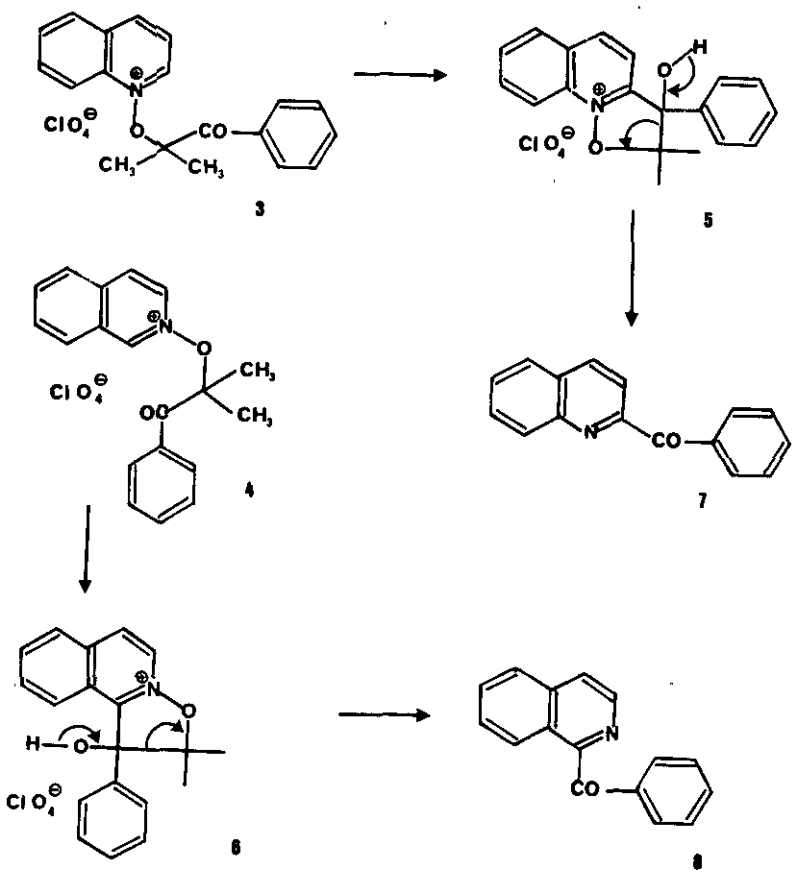
When the reaction was carried on salts bearing a keto group in their alkoxyl chain we were able to isolate the bicyclic isoxazolopyridinium salt resulting from the PARC phase of the above process[12]. In the case of the bicyclic intermediate 1, the subsequent ANRO phase was somewhat disfavoured by steric hindrance as well by electronic factors, owing to the presence of the methyl group, since this one lies in ortho position from that which would suffer the nucleophilic addition preceding the ring opening. So that a new decomposition competed with the ANRO phase and afforded 2-benzoyl-5-methylpyridine (2) as a by-product, the ring opening being still preferably observed.



This new mode of decomposition consisted in a fragmentation in acetone and a 2-acylpyridine, initiated by base deprotonation of the alcohol hydroxyl. It can be described as alkoxylogous of mode A as shown by the dotted lignes in the above scheme.

In order to observe only the new alkoxylogous path A decomposition, we have chosen a substrate for which ring opening would be more disfavoured. This appeared to be the case for N-alkoxyquinolinium and isoquinolinium salts which have not been shown to react according to path D during previous investigations[2]. For that purpose the N-alkoxyquinolinium and isoquinolinium salts 3 and 4 were prepared by reacting α-bromo isobutyrophenone with the corresponding N-oxides, in the presence of silver perchlorate, in acetonitrile solution[13]. These salts were submitted to decomposition by a secondary amine in methanol. In order to isolate the expected tricyclic isoxazolo quinolinium and isoquinolinium salts the reaction was performed in two steps. The PARC phase was realized using a crowded amine such as 2,2,6,6-tetramethylpiperidine which led to the tricyclic intermediates 5 and 6 with excellent yields[14]. A special mention can be made about the regioselective cyclization of the salt 4 which affords only the isoxazolo [2,3-a] isoquinoline derivative 6 and not its [2,3-b] isomer. This result shows that proton abstraction leading to the ylid occurs preferably at position-1 in accordance with the selectivity shown by deuteration in basic medium[15].

The subsequent fragmentation, alkoxylogous to mode A, was then performed by reacting these latter salts with piperidine which converted them in nearly quantitative yields to the benzoyl derivatives 7 and 8[16]. This result is indicative of the absence of any competitive mode of reaction with bases for these N-alkoxyl salts.



The overall sequence affords a new route to these compounds with an improved yield as compared to previous synthesis[17,18]. Further investigations are planned in order to generalize the present study to synthesis of various 2-acylquinolines and 1-acylisoquinolines as well as acyl derivatives of other aza heterocyclic compounds.

REFERENCES AND NOTES

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8. This base-induced deprotonation of N-alkoxypyridinium salts yielding ylids has been described by Abramovitch[9] as a fifth possible mode of reaction of these salts with nucleophiles (mode E).

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13. The salts 3 (oil) and 4 (mp : 129-130°C) obtained in 75 % and 95 % respective yield after 7 and 3 days at room temperature, were characterized by ir (KBr) 1690 (C=O), 1090 (ClO_4^-) cm^{-1}, and the following ^{1}H-nmr (DMSO d_6) data :

Compound 3 δ : 1.85 (6H, s, $(CH_3)_2$), 7.8-8.4 (10H, m, ArH), 9.40 (1H, d, H-8), 9.55 (1H, d, H-2).

Compound 4 δ : 1.85 (6H, s, $(CH_3)_2$), 7.5-7.8 and 8-8.8 (10H, m, ArH), 9.0 (1H, dd, H-3), 10.45 (1H, d, H-1).

14. The reaction was performed at room temperature for 24 h using one tenth of equivalent of the amine.

Compound 5 : yield 97 % ; mp 203-204°C ; ir (KBr) 3460 (OH) cm^{-1} ; 1H-nmr (DMSO d_6) δ : 1.20 (3H, s, CH_3), 1.80 (3H, s, CH_3), 7.50 (5H, s, phenyl), 7.95-8.75 (6H, m, ArH and OH), 9,35 (1H, d, H-9).

Compound 6 : yield 99 % ; mp 228-230°C ; ir (KBr) 3380 (OH) cm^{-1} ; ^{1}H-nmr (DMSO d_6) δ : 1.20 (3H, s, CH_3), 1.72 (3H, s, CH_3), 7.55 (5H, s, phenyl), 7.9-8.6 (5H, m, ArH+OH), 8.90 (1H, d, H-4), 9.20 (1H, d, H-9).

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16. The reaction was performed with 2 equivalents of piperidine at room temperature for 12 h. 2-benzoyl-quinoline 7 : yield 95 % ; mp 111°C (litterature : 110-111°C)[17] ; ir (KBr) 1670 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ : 7.2-8.4 (m, ArH).

1-benzoylisoquinoline 8 : yield 98 % ; mp 78-79°C (litterature : 78°C)[18] ; ir (KBr) 1670 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ : 7.35-8.25 (10H, m, ArH), 8.55 (1H, d, H-3).

All the crystallized compounds of this study gave satisfactory elemental analysis.

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