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New Route to Pyrido[1,2-*b*]pyridazinium Inner Salts. Evidence of a 1,3-Dipolar Cycloaddition-Ring Expansion Process

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Abstract:

2-Alkoxycarbonylpyridinium N-aminides behave as 1,3-dipoles when reacted with Michael acceptors, giving rise to the corresponding cycloadducts which, depending on their regioisomeric nature, subsequently undergo a ring expansion to give pyrido[1,2-*b*]pyridazinium inner salts.

Keywords: N-aminides; betaines; rearrangement; 1,3/1,4-dipoles

The heterocyclic mesomeric betaines [1] **1** are well established versatile 1,3-dipoles, which allows them to take part in 1,3-dipolar cycloaddition reactions [2]. 2-Alkyl and 2-amino substituted structures **2** have the potential to function as 1,4-dinucleophiles via deprotonation and are capable of reacting with 1,2-dicarbonyl compounds (Westphal reaction) [3] to give a variety of azonia derivatives possessing a quaternary bridgehead nitrogen [4-11]. By contrast, with the exception of a few examples [12-15] relatively less attention has been paid to the possibility of using ylides **3** as 1,4-nucleophile-electrophiles (Fig. 1).

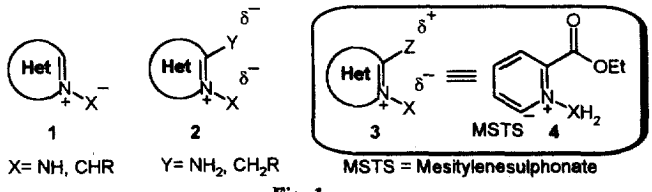

Fig. 1

With regard to the reactivity of **3**, we reported in a previous paper [16] a few examples of the 1,4-nucleophile-electrophile character of 2-ethoxycarbonyl azinium salts **4** which, on reaction with isocyanates and isothiocyanates gave rise to new conjugated mesomeric betaines

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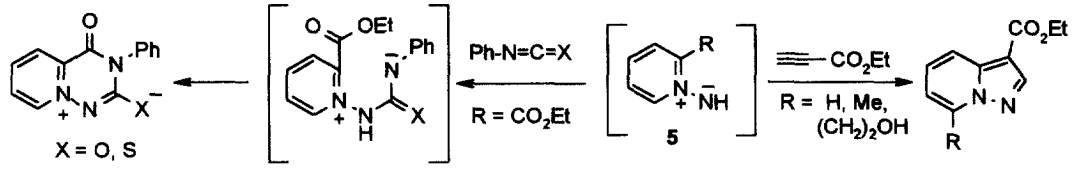
in a [4+2] cyclocondensation process. It has also been reported however, that the N-aminides **5**, behave as 1,3-dipoles when reacted with ethyl propiolate to afford the corresponding cycloadducts [17] (Scheme 1).



Scheme 1

This apparent dual role, prompted us to explore the reactivity of **4** with different olefinic dipolarophiles in order to gain insight into its behaviour. Initially we reacted N-methylmaleimide with **4** (X=N) in CH_2Cl_2, in the presence of *N*-diisopropylethylamine (Hünig's base) and we obtained, after consumption of **4** (2 h, r.t.), a mixture of the cycloadducts[1] **6** and **7** in 84% yield (2:3 ratio), along with traces of the heterobetaine **8**. Surprisingly, after 48 h reflux, the cyclocondensation product[2] **8** was obtained as the major component (49%), accompanied by minor amounts of the cycloadduct **6** (16%), as evidenced by ^{1}H NMR.

During attempts to characterize **7**, bidimensional t.l.c. experiments (silica gel, EtOAc/ MeOH) revealed that the cycloadduct **7** was easily transformed into the heterobetaine **8**. Furthermore, when **7** was isolated and heated in CH_2Cl_2 the heterobetaine **8** was also formed. However, under the same conditions the cycloadduct **6** extensively decomposes.

When unsymmetrical dipolarophiles were used an analogous behaviour was found, thus reaction of **4** with acrylonitrile afforded the heterobetaine **9a** as the only isolated product (86%) when the reaction was refluxed for 20 h. After the initial 15 min., t.l.c. showed the reaction mixture to contain adducts similar to **6** and **7**, together with **9a**. With longer periods, one of the cycloadducts (highest R_f, analogous to **7**) was seen to be transformed into **9a** as observed by bidimensional t.l.c.(silica gel, hexane: EtOAc, 1:1/ MeOH).

The scope of the process was tested with different Michael acceptors (Scheme 2) giving rise to mixtures of dihydroderivatives **9** and the fully aromatic compounds **10**. Furthermore, heterobetaines **9** were extensively transformed to **10** after 3 h reflux in CH_3CN.

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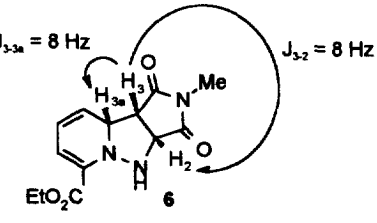
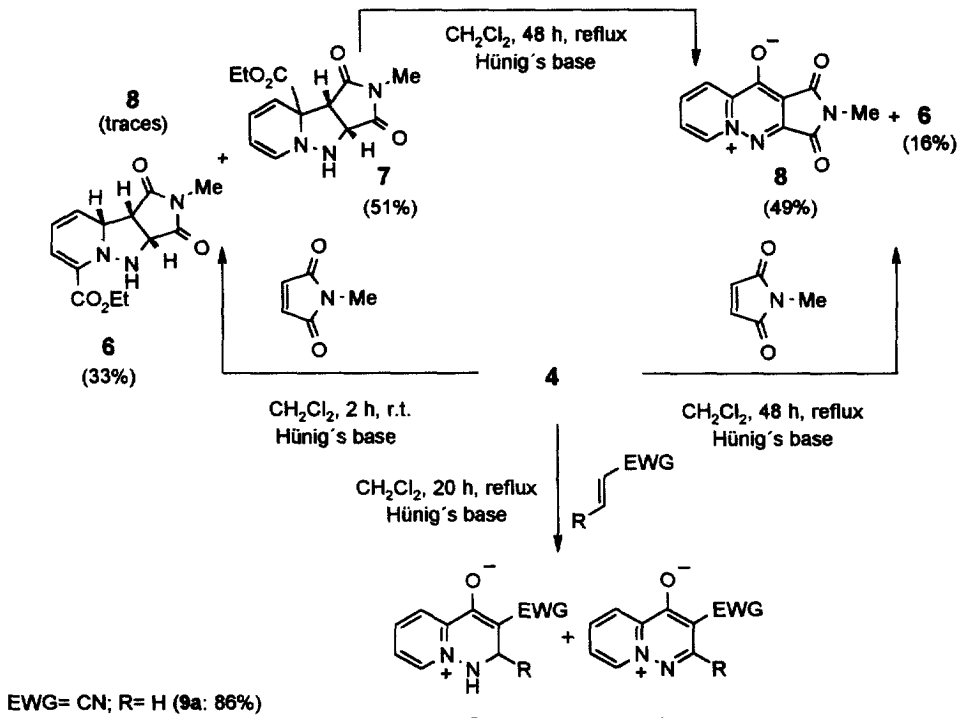
[1]The assigned structure of the major regioisomer **7** was established by ^{1}H NMR data on the basis of chemical shifts of the dihydropyridine moiety which show well-resolved signals for H_4-H_7. Similarly, the structure of the cycloadduct **6** derived from ^{1}H NMR was identified as the *endo*-cycloadduct. Coupling constants between H_3 and H_{3a} (8 Hz) as well as H_3 and H_2 (8 Hz) are consistent with a *cis* disposition for these hydrogens. Full characterisation of **6** and **7** was unambigously established by irradiation of the protons.

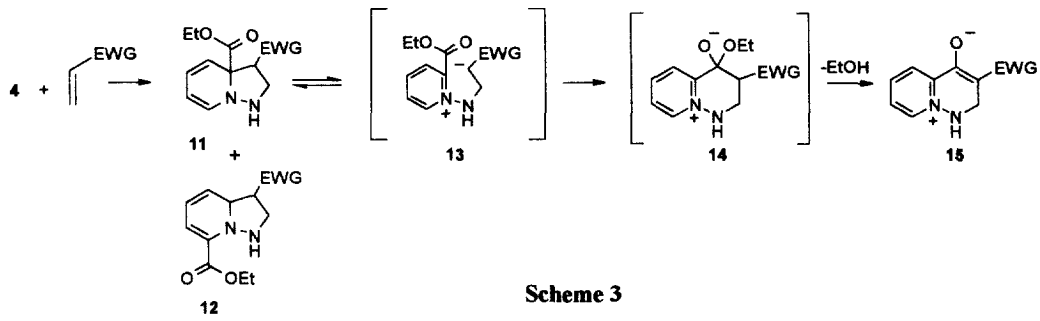




Scheme 2

To our knowledge, this is the first evidence of a cycloadduct ring expansion process, leading to the formation of conjugated mesomeric betaines. No doubt, the steric hindrance of the regioisomer **11** would favour rearrangement to the more stable system **15**, through a ring-opening process in which the dihydropyridine moiety regains aromaticity. Although the evolution of regioisomer **12**, is less clear, cycloreversion, oxidation or N-N bond cleavage should be involved [18].

[2]**General Procedure for the Preparation of Heterobetaines.** To a solution of the salt **4** (1 mmol) and the corresponding olefinic compound (1.1 mmol) in dry CH_2Cl_2 (10 mL), N-ethyldiisopropylamine (2 mmol) was added dropwise. After refluxing the reaction mixture for 48 h or 20 h, **8** and **9** were isolated by filtration and **10** were purified by chromatography (silica gel, acetone or acetone : EtOAc) from the filtrate. All new compounds described have satisfactory spectral and analytical data. For the compound **8**: mp >300 °C (DMF); IR (KBr) 1710, 1617, 1589, 1537, 1437, 1375 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) 9.39 (d, 1H, J = 6.6 Hz), 8.71 (d, 1H, J = 7.7 Hz), 8.42 (t, 1H, J = 7.7 Hz), 8.19-8.11 (m, 1H), 2.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 MHz) 165.2, 164.8, 161.1, 154.5, 147.6, 146.8, 142.3, 139.4, 127.4, 124.4, 23.5; MS (m/z) 229 (M^+, 55), 106 (55), 78 (100). Anal. Calcd for $C_{11}H_7N_3O_4$: C, 57.65; H, 3.08; N, 18.33. Found: C, 57.59; H, 3.29; N, 17.98.



Scheme 3

A theoretical study to establish whether the reaction pathway from the cycloadduct **11** to the heterobetaine **15** involves the intermediate **13** (Scheme 3), as was the case for the reaction of **4** with heterocumulenes, or proceeds throughout a concerted mechanism, is under investigation using *ab initio* techniques and the results will be the subject of a future report.

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