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New Base Induced Rearrangements of 4-Acylisoxazolidines. Anionic Reactional Cascades from Five Membered Rings to either Four Membered Rings or Open Chain Compounds.

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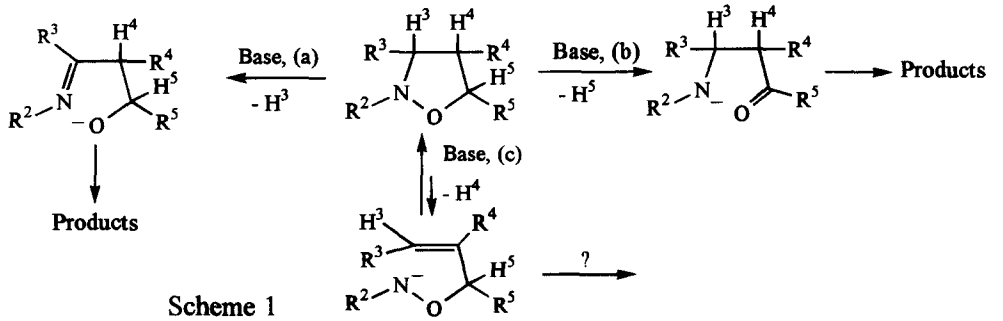
Abstract. Treatment of 2,3,3-triphenyl-4-formylisoxazolidines with bases triggers an unprecedented anionic reactional cascade which terminates with a 2-iminooxetane derivative. In the case of 2,3,3-triphenyl-4-methoxycarbonyl isoxazolidine the multistep rearrangement gives rise to a derivative of malonic acid.

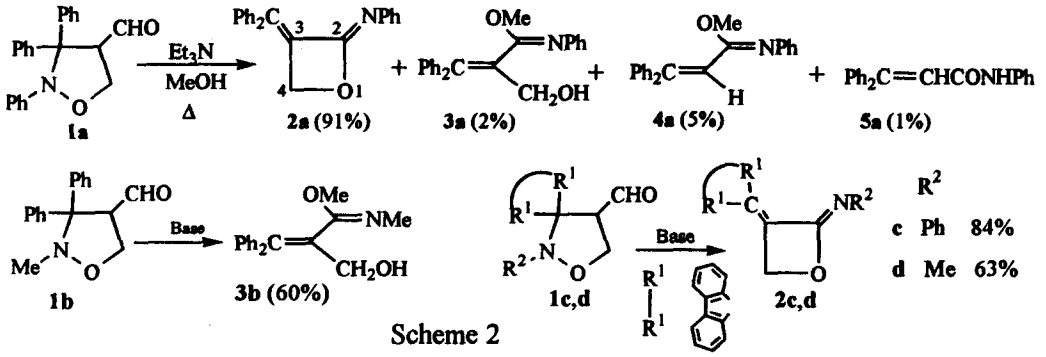
Isoxazolidines have progressively been emerging as important building blocks in the field of natural product synthesis.[1] Their use in this field profits highly from the easy cleavage of their weak N-O bond. In fact, the low dissociation energy of this bond has driven the hydrogenolytic, homolytic and heterolytic ring-opening of isoxazolidines reported so far.[1] In particular, abstraction of an acidic proton from position 5 [(b), Scheme 1][1,2] and position 3 [(a)][1,2a] brings about fast heterolytic cleavage of the N-O bond.[3] On the other hand, the presence of an electron withdrawing group at position 4 can, in principle, open a new reaction channel, namely, a retro-Michael reaction with abstraction of H-4 and C-3/N bond cleavage [(c)]. This latter reaction is certainly reversible and, actually, only epimerization or H/D exchange has been reported for the 4-acylisoxazolidines investigated so far.[2a,2d]



Scheme 1

We report here that, indeed, the retro-Michael reaction not only is a viable mechanism for properly substituted isoxazolidines, but also that it triggers interesting reactional cascades.

Treatment of 2,3,3-triphenyl-4-formylisoxazolidine (**1a**)[4] with triethylamine in refluxing methanol (MeOH/Et_3N = 10:1) for 6 hours resulted in formation of the 2-(phenylimino)oxetane (**2a**) which crystallized from the reaction mixture at -8 °C in very good yields (≥ 85%) as beautiful slightly yellow prisms. A careful chromatography of the mother liquors allowed the quantitative account of the material balance by isolating further amounts of **3a** and minor amounts of acyclic products, i.e., **3a**, **4a** and **5a** (Scheme 2).[5-8]



Scheme 2

The structure of **2a** was inferred from spectroscopic data[7] and straightforward chemical reactions.[8] However, given that compound **2a** looked quite unexpected as a reaction product of **1a**, its structure was established by single crystal X-ray analysis[9] (Figure).

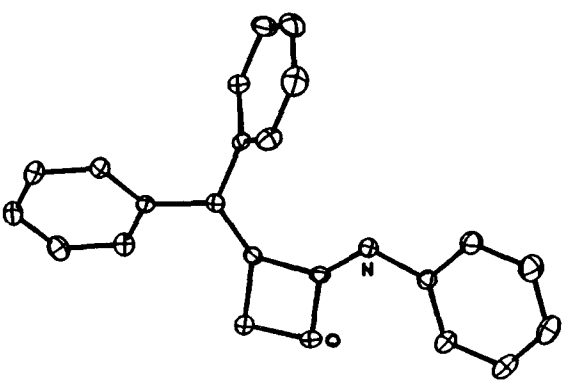
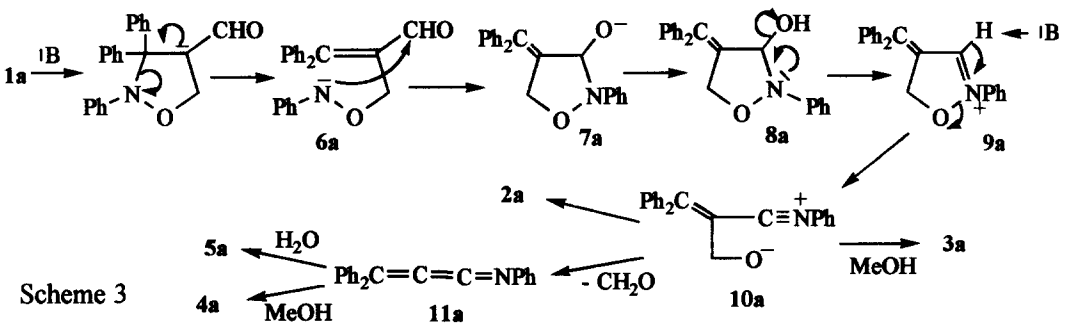


Figure. A perspective view of compound **2a**.

Good yields of iminooxetane derivatives, i.e., **2c** and **2d**,[7] were also isolated from the base catalyzed (MeOH/Et_3N under reflux) rearrangements of **1c**[4] (9 hours) and **1d**[4] (23 h) whilst only the open chain compound **3b**[8] could be detected and isolated in the case of the reaction of **1b**[4] (3 h) (Scheme 2).

As for the mechanism of the rearrangement (Scheme 3), abstraction of the proton from position 4 of **1a** is followed by a retro-Michael reaction to give **6a**, which in turn ring closes to **7a** through nucleophilic attack by the anionic moiety on the formyl group. Formation of the isoxazolinium salt **9a** from **8a** by elimination of hydroxyl ion can find an analogy in the formation of iminium ions as intermediates in the reduction of tertiary amides with $LiAlH_4$ and in the uncatalyzed formation of imines from primary amines

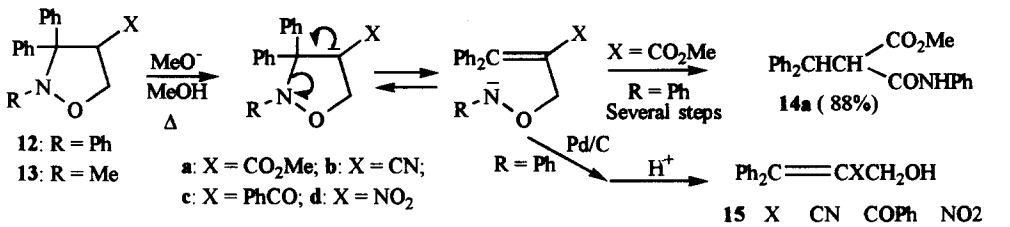
and carbonyl compounds[10] while ring opening of **9a** by base resembles the well known base induced opening of isoxazolium salts.[11] Ring closure of **10a** affords the iminooxetane **2a** while the minor reaction pathway to **4a** and **5a** reasonably involves loss of formaldehyde and formation of the cumulene **11a**. The imino ether **3a** is derived from trapping of **10a** by MeOH.[12]



Scheme 3

In the case of the reaction of **1b**, surprisingly, the intermolecular trapping of the zwitterion of type **10** by MeOH to give **3b** seems to fully overcome ring closure to the 2-(methylimino)oxetane derivative as TLC analysis, yet from the very beginning of the reaction, showed only the presence of **3b.**

A different behavior was observed when the formyl group was replaced by other electron attracting substituents (Scheme 4). For example, a deep-seated base (sodium methoxide in methanol at reflux for 24 hours) induced rearrangement was observed in the case of **12a**[4] (X = CO_2Me) which, however, afforded high yields of an open chain derivative, i.e., **14a**. In the case of **12b-d**[4] only the retro-Michael reaction was operative in the presence of sodium methoxide, and compounds **15b-d** were isolated in variable yields after treatment of the crude reaction mixture with Pd/C and neutralization.



Scheme 4

Finally, in the case of compounds **13b**[4] and **13d**[4] no ring opening but only H/D exchange was observed upon treatment with sodium methoxide in deuteromethanol.

We are now engaged in clarifying the mechanistic details of formation of both compounds **2a**, **2c**, **2d** and **14a** as well as in investigating the reaction of other derivatives in order to assess more precisely the scope and limits of these unprecedented base induced rearrangements of isoxazolidines bearing electron-withdrawing groups at position 4. The results reported above suggest that there are interesting synthetic possibilities, in particular in the field of heterocyclic chemistry, still hidden which certainly deserve further investigation.

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3. For base induced opening of isoxazolidinium salts see reference 1 and Casuscelli, F.; Chiacchio, U.; Rescifina, A.; Romeo, R.; Romeo, G.; Tommasini, S.; Uccella, N. *Tetrahedron*, **1995**, *51*, 2979-2990.
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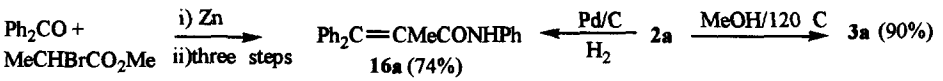
5. Similar results were obtained by using sodium methoxide as base in methanol (r.t., 24 h).
6. All compounds were fully characterized by analytical and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR and mass spectra)[7] as well as chemical reactions.[8]
7. **2a**: m.p. 134-135 °C; IR,ν_{max} (nujol) = 1685 cm^{-1}; ^{1}H NMR, δ ($CDCl_3$) 5.01 (s, 2 H , CH_2); ^{13}C NMR, δ ($CDCl_3$) 71.8 (t, C-4), 155.6 (s, C-2); mass spectrum, m/z (75 eV) 311 (73%, $M^{+\cdot}$), 192 (100%, $Ph_2C{=}C{=}CH_2^{+\cdot}$), 191 (83%). Very similar spectroscopic data were exhibited by **2c** (yellow needles from MeOH, m.p. 160-162 °C) and **2d**. (yellow needles from MeOH, m.p. 139-140 °C).
8. In particular, **2a** was catalytically hydrogenated to **16a** which in turn was easily and unambiguously synthesized starting from a Reformatsky reaction between benzophenone and methyl α-bromopropionate.



The imino ether **4a** (colorless crystals, m.p. 89-92 °C) was hydrolyzed under acidic conditions to $Ph_2C{=}CHCO_2Me$. This compound was also prepared starting from the Reformatsky reaction between benzophenone and methyl bromoacetate and easily transformed into **5a**.[13] Catalytic hydrogenation of **4a** led to $Ph_2CH\text{-}CH_2CONHPh$ (colorless needles from benzene/cyclohexane, m.p. 176-178 °C) which in turn was obtained from **14a** [colorless needles from benzene, m.p. 200-203 °C; IR,ν_{max} (nujol) = 3290, 1741 and 1648 cm^{-1}; ^{1}H NMR, δ ($CDCl_3$) 3.56 (s, OMe), 4.29 (d, 1 H, CH, J = 12.0 Hz), 4.77 (d, 1 H, CH, J = 12.0 Hz), 7.25 (m, 15 H, aromatic protons), 7.93 (broad s, 1 H, NH) ; ^{13}C NMR, δ ($CDCl_3$) 52.6 (q), 52.8 (d), 60.0 (d), 164.3 (s), 170.5 (s)] by basic hydrolysis of the ester moiety and decarboxylation of the resulting acid.

The imino ether **3b** (colorless prisms from cyclohexane, m.p. 139-140 °C) was hydrolyzed under acidic conditions to $Ph_2C{=}C(CH_2OH)(CONHMe)$ (colorless leaflets from $MeOH/H_2O$, m.p. 167-169 °C).

9. **2a**: Orthorombic, space group *Pbca*; *a* = 17.250, b = 19.724, *c* = 9.805 Å; D_C = 1.24 g/cm^3; F(000) = 1312; μ = 5.60 cm^{-1}. Bond distances (Å) : $N{=}C_2$ = 1.254, $O_1\text{-}C_2$ = 1.404, $C_2\text{-}C_3$ = 1.482, $C_3\text{-}C_4$ = 1.514, $C{=}C_4$ = 1.339. Bond angles(°): $O_1\text{-}C_2\text{-}C_3$ = 92.9, $C_2\text{-}C_3\text{-}C_4$ = 87.0, $C_3\text{-}C_4\text{-}O_1$ = 88.7, $C_4\text{-}O_1\text{-}C_2$ = 91.3, $N\text{-}C_2\text{-}C_3$ = 136.5, $C_2\text{-}C_3\text{-}C$ = 137.1. Torsion angles(°): $O_1\text{-}C_2\text{-}C_3\text{-}C_4$ = -1.6, $C_2\text{-}C_3\text{-}C_4\text{-}O_1$ = 1.5, $C_3\text{-}C_4\text{-}O_1\text{-}C_2$ = -1.6, $C_4\text{-}O_1\text{-}C_2\text{-}C_3$ = 1.6, $N\text{-}C_2\text{-}C_3\text{-}C$ = -3.9.
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