ONE POT *EXO-ENDO* ISOMERIZATION IN BICYCLIC ADDUCTS ARISING FROM 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 7-OXA-NORBORNENE DERIVATIVES

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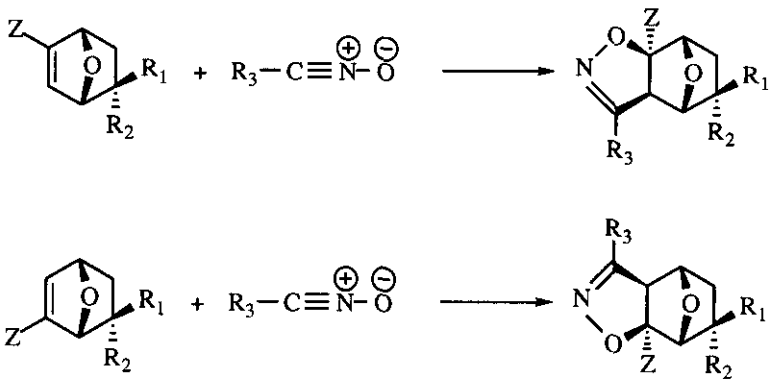
Dedicated to Prof. Rolf Huisgen with occasion of his 75th birthday

Abstract -A new, one pot methodology to carry out the *exo-endo* isomerization of some tricyclic adducts derived from the cycloaddition of 7-oxabicyclo[2.2.1]hept-5-ene derivatives and nitrile oxides is described.

The 1,3-dipolar cycloaddition reactions of several 1,3-dipoles and bicyclic, strained olefins display a totally *exo* selectivity[1] in absence of other factors as, for instance, hydrogen bonding.[2] In the case of 7-oxabicyclo[2.2.1]heptene derivatives the rule was invariably observed in the cycloaddition of nitrile oxides and imines,[3] nitrones,[4] azides[5] and diazoalkanes.[6] Due to the high synthetic potential of the adducts of nitrile oxide and alkenes,[7] the possibility of the *exo-endo* isomerization of the adducts resulting from cycloaddition of nitrile oxides and 7-oxanorbornene derivatives could increase the utility of this reaction[8] considering moreover that the regioselectivity of the process is governed by the nature of the substituents attached to the double bond of the bicyclic system.[3]

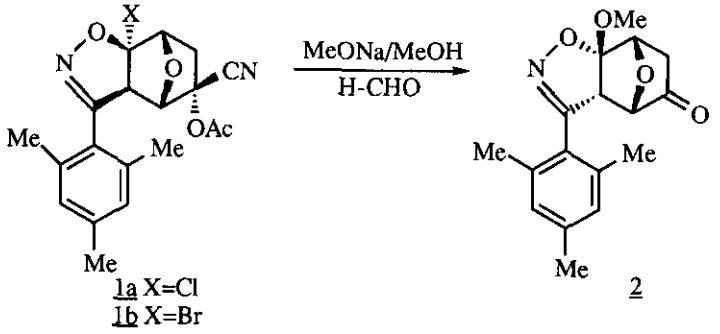
To the best of our knowledge, only two cases of *exo-endo* isomerizations in related systems have been described. Firstly, Huisgen *et al.* reported the *exo-endo* isomerization of the product obtained in the reaction of norbornene with diphenylnitrilimine.[9] A more recent example has been observed in the case of a norbornene annulated cyclopentanone.[10] No cases have been published in oxanorbornenic ring systems or for nitrile oxide cycloadducts.



R_1, R_2 = OCH_2CH_2O; R_1 = CN; R_2 = OAc; R_1, R_2 = O; R_1 = H; R_2 = CH_2OBn

Z = Cl, Br, $PhSO_2$; R_3= C_6H_5, Me, 2,4,6-$Me_3C_6H_2$.

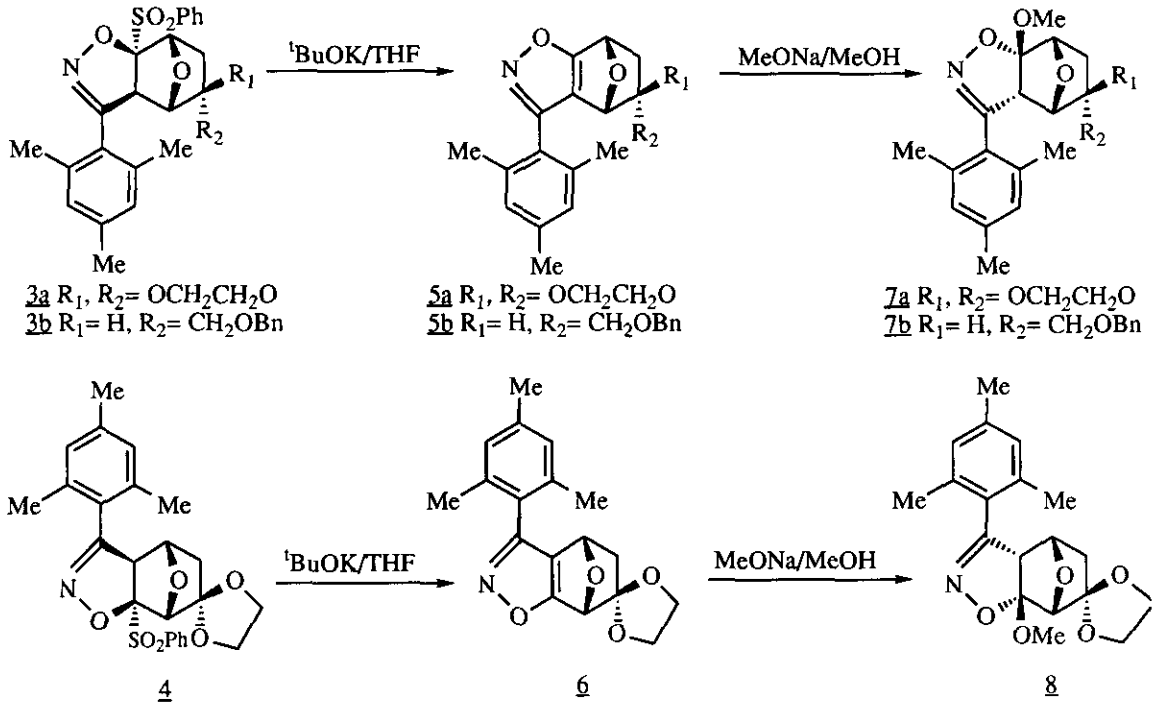
The reactions of haloadducts (1a) and (1b), obtained previously by us,[3] with MeONa/MeOH (room temperature, 48 h) affords compound (2) (75% isolated yield from 1a and 90% isolated yield from 1b) with concomitant hydrolysis of the cyanoacetoxy functional group.[11]



1a X=Cl
1b X=Br

2

Regarding the reaction pathway we speculate with the possibility that the isoxazole could be an intermediate of the process. All attemps of isolation of this compound from the halo derivatives (1) in the reaction conditions previously indicated were unsuccesful. However, reactions of the sulfones (3) and (4) [3] with $^tBuOK/THF$ (room temperature, 4 h, 95-98% isolated yield) gave the isoxazoles (5) and (6) respectively. Treatment of these compounds with MeONa/MeOH in the same conditions as for the isomerization of compounds (1) affords the adducts (7) and (8) (90-100% isolated yields).[12]



Thus, the isoxazole appears to be a discrete intermediate in the isomerization process. The nucleophilic reaction on this planar heterocyclic ring system occurs with total *exo* selectivity and regioselectivity resulting from the attack on the less hindered position of the isoxazole moiety.

The regio- and stereochemistries of the products were readily established by ^{1}H-nmr spectrocopy.[12] For instance, in the *endo* isomers, H-5 for (8) and H-6 for (2), (7a), and (7b) presented quite different splitting patterns (d, J = 6.5 Hz; or dd, J = 6.5, 1.3 Hz)), from the corresponding singlets for the same protons in the *exo* isomers, due to the absence of coupling with H-1 or H-4 in the *exo* isomers.[3]

In conclusion we have developed a new, simple, one pot methodology for the *exo-endo* isomerization of the tricyclic adducts derived from 7-oxanorbornenic compounds and nitrile oxides.

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12. All new products had satisfactory spectral and analytical data. For instance, 5a: mp 124-125 °C; ir (KBr) ν_{max} 2900, 1600, 1580, 1450, 1320, 1020, 900; ^{1}H-nmr ($CDCl_3$), δ 1.86 (1H, d, J = 12.5 Hz, H-3n), 2.21 (6H, s, $2CH_3$), 2.32 (3H, s, CH_3), 2.48 (1H, dd, J = 5.1, 12.5 Hz, H-3x), 3.64 (1H, m, CH_2), 3.79 (2H, m, CH_2), 4.02 (1H, m, CH_2), 4.58 (1H, s, H-1), 5.37 (1H, d, J = 5.1 Hz, H-4), 6.92 (2H, s, H-Ar); ^{13}C-nmr ($CDCl_3$), δ 20.0, 21.1, 39.8, 65.0, 70.5, 76.5, 115.5, 124.5, 128.3, 137.7, 138.9, 156.7, 185.6. Anal. Calcd for $C_{18}H_{19}NO_4$, C, 68.00; H, 6.11; N, 4.47. Found, C, 67.88; H; 6.08; N; 4.52. 7a: mp 114-115 °C; ir (KBr) ν_{max} 2960, 2930, 1610, 1450, 1345, 1220, 1130, 1020; ^{1}H-nmr ($CDCl_3$), δ 2.18 (1H, ddd, J = 13.8, 6.5, 1.2 Hz, H-3x), 2.27 (3H, s, CH_3), 2.40 (1H, d, J = 13.8 Hz, H-3n), 2.49 (6H, s, $2CH_3$), 3.14

(1H, m, CH_2), 3.41 (3H, s, OCH_3), 3.68 (2H, m, CH_2), 3.88 (1H, m, CH_2), 4.20 (1H, ddd, J = 6.5, 1.3, 1.2 Hz, H-1), 4.40 (1H, dd, J = 6.5, 1.3 Hz, H-6), 4.63 (1H, dm, J = 6.5, 1.3, 1.3 Hz, H-4), 6.90 (2H, s, H-Ar); ^{13}C-nmr ($CDCl_3$), δ 20.9, 22.9, 36.0, 50.6, 60.7, 63.7, 65.0, 81.7, 83.8, 113.0, 121.0, 125.3, 130.1, 137.7, 138.3, 156.2. Anal. Calcd for $C_{19}H_{23}NO_5$, C, 66.07; H, 6.71; N, 4.06. Found, C, 65.95; H; 6.60; N; 4.00.

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