Notes

Difunctionalized 4-Nitroisoxazoles as Synthetic Equivalents of the Corresponding 4,5-Didehydro Derivative in [2 + 4] Cycloadditions with 2,3-Dimethylbuta-1,3-diene: Reductive Eliminations of the Activating Groups from the Primary Adducts[1]

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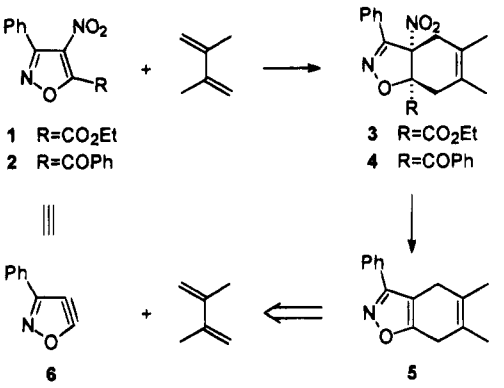
Beyond their theoretical interest as labile intermediates, arynes play a significant role in organic synthesis: an increasing variety of polynuclear ring systems have been obtained from these species over the past decades by cyclization and cycloaddition processes.[2] However, only a few six-membered heterocyclic counterparts such as simple and condensed didehydropyridines have been employed in similar reactions.[3] The possibility of exploiting five-membered hetarynes for the same purposes was almost completely disregarded, probably due to the difficulties connected with their generation,[3a] and the search of suitable equivalents for the latter intermediates could be of interest both from a mechanistic and synthetic viewpoint.

In this context, the equivalence of N-benzensulfonylated β-nitropyrrole and β-nitroindole with the corresponding 2,3-didehydro compounds may be inferred from a report on the Diels–Alder reactions of the former products with isoprene, followed by thermal extrusion of nitrous acid from the primary adducts.[4] Analogously, 5-unsubstituted 4-nitroisoxazoles were recently found to behave as 4,5-didehydroderivatives in their reactions with some 1,3-dipoles[5] and dienes.[6]

On the other hand, previous results from our laboratory showed that the activated C(4)–C(5) double bond of the title compounds **1** and **2** easily undergoes [2 + 4] cycloadditions with an excess of 2,3-dimethylbuta-1,3-diene (DMB) to give the bicyclic systems **3** and **4**, respectively, in good yields together with small amounts of the corresponding dihydro-1,2-benzisoxazole **5**.[7]

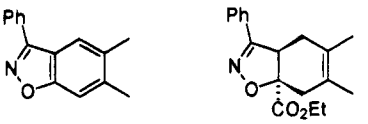
Scheme 1



The latter derivative, arising from **3** and **4** through reductive eliminations of the electron-withdrawing groups, can also be regarded as the [2 + 4] cycloaddition product of DMB and the hetaryne **6**. In order to gain better insight into these conversions, and to establish the best experimental conditions for attaining the desired equivalence of the starting materials with **6** (Scheme 1), we undertook a detailed study of the above elimination processes.

Results and Discussion

Some striking preliminary results on the thermal behavior of the cycloadduct **3**[1] were confirmed by further experiments: whereas this compound fully decomposed in xylene at 150 °C, it was converted into **5** and the corresponding aromatization product **7** in 59% and 14% yields, respectively, by treatment with an excess of DMB under the same conditions (Table 1, entries 1 and 2).



The loss of NO_2 and CO_2Et in the latter reaction is certainly due to a peculiar role of the diene: it probably acts as a suitable scavenger of reactive elimination fragments that could be responsible, if not trapped, for subsequent more complex pathways. This tentative explanation appears to be supported by the comparable results obtained by replacement of DMB with different alkenes such as cyclohexene, norbornene, and 2,3-dimethylbut-2-ene.

A quite different reaction pattern was observed for the nitro ketone **4** leading, under the original conditions, to the bicyclic system **7** in 68% yield, together with a small amount (6%) of **5** (entry 3).

This finding can be accounted for on the basis of a concerted intramolecular removal of the *cis* nitro and

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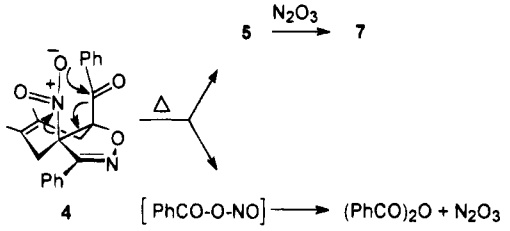
Table 1. Reductive Eliminations on the Nitro Derivatives 3 and 4

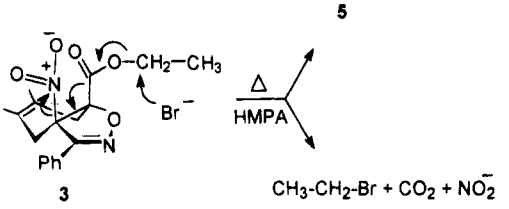
entry	adduct	solvent	reagent	temp (°C)	time (h)	yield (%) 5[a]	7[a]	8[a]
1	**3**	xylene		150	7			
2	**3**	xylene	DMB	150	7	59	14	
3	**4**	xylene		150	7	6	68	
4	**4**	xylene	DMB	150	7	75	16	
5	**3**	HMPA	NaBr	120	2	70	10	
6	**3**	benzene	Bu_3SnH–AIBN	80	4	8[b]	4[b]	60[b]
7	**4**	benzene	Bu_3SnH–AIBN	80	2	90	traces[c]	
8	**3**	benzene	$(Bu_3Sn)_2$–$h\nu$	80	24	36[b]	9[b]	
9	**4**	benzene	$(Bu_3Sn)_2$–$h\nu$	80	4	76	15	

[a] Isolated yields. [b] Isolated yields based on the recovered starting material. [c] Observed by ^1H NMR in the reaction mixture.

Scheme 2



Scheme 3



benzoyl groups from the substrate, induced by an attack of the NO_2 oxygen on the remarkably electrophilic CO carbon. The resulting five-membered transition state evolves into **5** and benzoyl nitrite through a pericyclic process that, to the best of our knowledge, is unheard of in the chemistry of reductive eliminations (Scheme 2). Oxidation of **5** by dinitrogen trioxide, generated by thermal decomposition of benzoyl nitrite,[8] could then account for the formation of **7**.

The mechanistic rationale advanced above agrees well with the following experimental data:

(a) Mass spectral analysis allowed us to detect the presence of benzoic anhydride and the corresponding acid in the reaction mixture.

(b) Nearly equimolecular amounts of **5** and **7** were present in the crude product (^1H NMR) after addition of urea (molar ratio 1:5) that partially competes with the former compound in consuming N_2O_3.

(c) When the thermolysis was carried out in the presence of an excess of DMB, we isolated the same products in 75% and 16% yields, respectively (entry 4); the predominant trapping of the oxidizing agent by the diene largely ensures in this case the survival of the primary elimination product.

A detailed investigation by Ono and co-workers demonstrated that alkene formation via dealkoxycarbonylation and denitration can be advantageously performed with sodium bromide in HMPA at 120–150 °C. Under these conditions, variously functionalized open-chain β-nitro esters were converted into the corresponding α,β-unsaturated compounds by synchronous *anti* elimination processes.[9]

Following the same procedure, we obtained **5** from the adduct **3** in good yield (entry 5), likely through the *syn* version of the E2 mechanism cited above (Scheme 3).

Since the pioneering works of Japanese and American groups,[10] tributyltin hydride has been extensively used as an excellent tool for carrying out selective denitrohydrogenation of various aliphatic nitro compounds.[11] It has also been successfully exploited for new general alkene syntheses based on reductive eliminations from vicinal dinitro compounds, β-nitro sulfones, and β-nitro sulfides.[11] These reports prompted us to test the reactivity of Bu_3SnH toward adducts **3** and **4** containing a vicinal NO_2/CO_2Et and $NO_2/COPh$ moiety, respectively.

When compound **3** was refluxed with a small excess of Bu_3SnH and a catalytic amount of AIBN in anhydrous benzene, **5** and **7** were isolated in very poor yields, the predominant product being the bicyclic ester **8**. On the contrary, the nitro ketone **4** reacted under the same conditions, affording nearly quantitatively the desired derivative **5** that was isolated in 90% yield (entries 6 and 7).

According to the mechanism recently established for the above denitration reactions,[12] our results are plausibly accounted for by the sequences depicted in Scheme 4. The ((tributylstannyl)oxy)nitroxyl radicals **9** and **10** represent in both instances the key intermediates, but their subsequent behavior critically depends on the nature of the R group. The prevalent formation of **8** from **3** certainly involves the preferential routes a and b, whereas the small amount of **5** can arise from **11** or, alternatively, by a concerted *syn* elimination from the precursor **9** (route c). The later pathway becomes the exclusive one for the corresponding species **10** containing a more electrophilic CO carbon, and the exceptionally clear conversion of **4** into **5** is characterized in the second step by a mechanistic pattern greatly resembling that previously emphasized for the thermal reaction of the nitro ketone adduct. The resulting chain process, sustained by $Bu_3Sn^\bullet$, appears to be supported by the possibility of achieving similar results from **4** and a 0.1 molar equiv of Bu_3SnH.

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(9) Ono, N.; Tamura, R.; Eto, H.; Hamamoto, I.; Nakatsuka, T.; Hayami, J.; Kaji, A. *J. Org. Chem.* **1983**, *48*, 3678.
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(11) For a comprehensive review on these topics, see: Ono, N. In *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; Feuer, H., Nielsen, T. N., Eds.; VCH Publishers: New York, 1990; Chapter 1.
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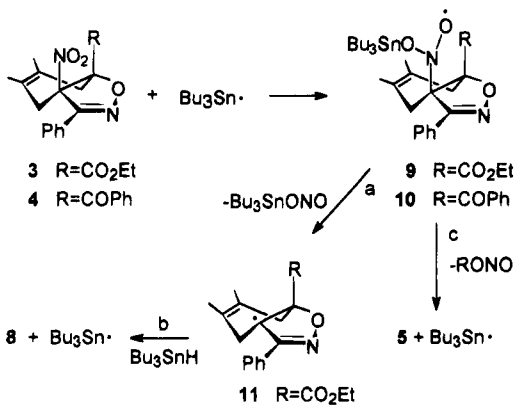
Scheme 4



Finally, in order to suppress the denitrohydrogenation process in favor of the elimination one, the same radical was generated from hexabutylditin. This procedure worked again very well with **4**, but only partially satisfactory results were obtained for **3** which showed a remarkably lower and more complex reactivity, affording compounds **5** and **7** in 36% and 9% yields, respectively (entries 8 and 9).

In summary, the above results clearly prove that suitably functionalized 4-nitroisoxazoles represent useful synthetic equivalents of the corresponding hetaryne for Diels–Alder reactions with DMB. Depending on the nature of the substituent at position 5, the equivalence can be optimized by resorting to already tried or unprecedented reductive eliminations processes.

We believe that this attractive tandem methodology can serve as a useful model for further investigations on the behavior of other heterocyclic nitro compounds.

Experimental Section

General. Chromatographic experiments and spectroscopic measurements were made as reported recently.[5]

Thermal Reactions of the Adducts 3 and 4 in the Presence of DMB. General Procedure. A mixture of the nitro derivative (0.5 mmol) and the diene (0.205 g, 0.281 mL, 2.5 mmol) in xylene (1 mL) was heated in a sealed tube at 150 °C until the starting material disappeared (TLC, ^{1}H NMR). Evaporation of the mixture to dryness under reduced pressure left a residue which was subjected to flash chromatography with toluene as eluent.

A. The crude product **3** afforded 5,6-dimethyl-3-phenyl-1,2-benzisoxazole (**7**) (R_f = 0.57, 0.016 g, 14%) that was sublimed at 40 °C (10^{-2} Torr) to give colorless crystals: mp 61–62 °C (lit.[13] mp 63 °C); IR 3060, 2980, 2920, 1620, 1490, 1420, and 1355 cm^{-1}; ^{1}H NMR δ 2.35 (s, 3H), 2.38 (s, 3H), 7.35–7.70 (m, 5H), 7.90–8.15 (m, 2H); ^{13}C NMR δ 19.9 (q), 20.7 (q), 110.1 (d), 118.4 (s), 121.35 (d), 127.9 (d), 128.9 (d), 129.2 (s), 129.9 (d), 132.9 (s), 139.9 (s), 156.6 (s), 163.1 (s).

The slower moving band gave compound **5**[7] (R_f = 0.41, 0.067 g, 59%).

B. The reaction product of **4** yielded the bicyclic derivatives **5** (0.085 g, 75%) and **7** (0.018 g, 16%).

Thermolysis of the Nitro Ketone 4. Operating as above, the residue from the thermal reaction of **4** in the absence of DMB afforded **5** (0.007 g, 6%) and **7** (0.076 g, 68%).

Reaction of the Nitro Ester 3 with NaBr. A mixture of compound **3** (0.344 g, 1 mmol) and NaBr (0.113 g, 1.1 mmol) in HMPA (2 mL) was stirred at 120 °C for 2 h; chromatographic workup of the gummy product obtained by treatment of the resulting solution with ice–water (10 mL) gave **5** (0.158 g, 70%) and **7** (0.022 g, 10%).

Reactions of 3 and 4 with Tributyltin Hydride. General Procedure. Bu_3SnH (0.218 g, 0.20 mL, 0.75 mmol) and AIBN (0.010 g, 0.055 mmol) were added under nitrogen to the cycloadduct (0.5 mmol) in anhydrous benzene (10 mL), and the mixture was refluxed for the time indicated in Table 1. Removal of the solvent under reduced pressure left a residue that was purified by flash chromatography.

A. Chromatographic resolution of the reaction product of **3** [toluene/ethyl acetate (40:1 v/v) as eluent] afforded, in order of decreasing mobility, the benzisoxazole **7** (R_f = 0.70, 0.004 g, 4%), the dihydro derivative **5** (R_f = 0.62, 0.008 g, 8%), the starting nitro compound (R_f = 0.47, 0.018 g), and ethyl (3a*RS*,7a*RS*)-5,6-dimethyl-3-phenyl-3a,4,7,7a-tetrahydro-1,2-benzisoxazole-7a-carboxylate (**8**) (R_f = 0.28, 0.080 g, 60%) as a pale yellow oil that was purified by dissolution in ether, filtration, evaporation to dryness, and prolonged evacuation at room temperature (10^{-2} Torr): IR (liquid film) 1735 cm^{-1}; ^{1}H NMR δ 1.31 (t, J = 7 Hz, 3H), 1.53 (br s, 3H), 1.76 (br s, 3H), 2.20 (dd, J = 15 and 3.7 Hz, 1H), 2.36 (dd, J = 15 and 7 Hz, 1H), 2.44–2.65 (AB system, J_{AB} = 15 Hz, 2H), 4.25 (qd, J = 7 and 1.2 Hz, 2H), 4.26 (dd, J = 7 and 3.7 Hz, 1H), 7.35–7.44 (m, 3H), 7.60–7.70 (m, 2H); ^{13}C NMR δ 14.0 (q), 19.1 (q), 19.5 (q), 31.3 (t), 36.8 (t), 50.5 (d), 61.9 (t), 90.2 (s), 125.2 (s), 125.9 (s), 127.1 (d), 128.5 (s), 128.7 (d), 130.0 (d), 159.1 (s), 172.6 (s). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.88; H, 6.85; N, 4.46.

B. The crude product obtained from **4** was purified chromatographically with petroleum ether/ethyl acetate (8:1 v/v) as eluent to give compound **5** (0.101 g, 90%).

Reactions of 3 and 4 with Hexabutylditin. General Procedure. A mixture of the adduct (0.5 mmol) and the tin reagent (0.29 g, 0.25 mL, 0.5 mmol) in the same solvent (2 mL) was irradiated under nitrogen with a 250-W sun lamp kept at a distance of ca. 2 cm from the reaction vessel in order to ensure a gentle refluxing for the time reported in Table 1; the crude product, obtained as above, was worked up chromatographically (toluene as eluent).

A. Compounds **5** (0.034 g, 36%) and **7** (0.009 g, 9%) were isolated together with some unreacted **3** (0.026 g).

B. The reaction product of **4** afforded **5** (0.085 g, 76%) and **7** (0.017 g, 15%).

Acknowledgment. We wish to thank Mrs. Brunella Innocenti for the analytical data.

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