18. A Novel Nitrone Cycloaddition/Rearrangement

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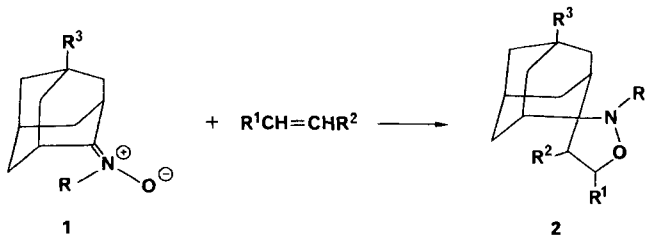
(8.VIII.89)

Adamantanone-derived nitrone **4** and some other keto-nitrones, when reacted with aromatic and aliphatic aldehydes in refluxing toluene or tetrahydrofuran, formed the corresponding aldonitrones (*Z*)-**10**, the latter arising from the fragmentation of an initially formed 1,4,2-dioxazolidine **6** to adamantan-2-one and an oxaziridine intermediate **11**, which then rearranges to (*Z*)-**10**.

Introduction. – In [1], we reported the preparation of a series of novel substituted spiro[isoxazolidine-3,2′-tricyclo[3.3.1.1^{3,7}]decane] derivatives **2** through the intermediacy of the adamantane-derived nitrone precursors **1** *(Scheme 1)*. The 1,3-dipolar cycloaddition [2][3] of **1** and various substituted olefins yielded the corresponding spiro-isoxazolidines **2**.

Scheme 1

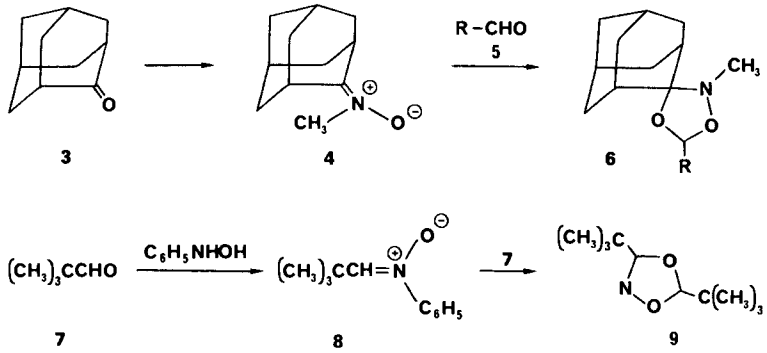


1 **2**

Nitrones (= alkylideneamine *N*-oxides) are known for their ability to undergo nucleophilic attack in the presence of bases [4][5]. However, the tendency of nitrones to serve as 4 π-addends in cycloadditions with a broad spectrum of dipolarophiles [5] provides also valuable synthetic applications, especially for the synthesis of a great number of natural products [6–9]. We envisioned to further extend our previous efforts in this direction by attempting the synthesis of a novel heterocyclic system, the spiro[1,4,2-dioxazolidine-3,2′-tricyclo[3.3.1.1^{3,7}]decane] [6], starting with *N*-(adamantanylidene)methylamine *N*-oxide (**4**; obtained from **3**) and an appropriate aldehyde **5** as the required dipolarophile *(Scheme 2)*.

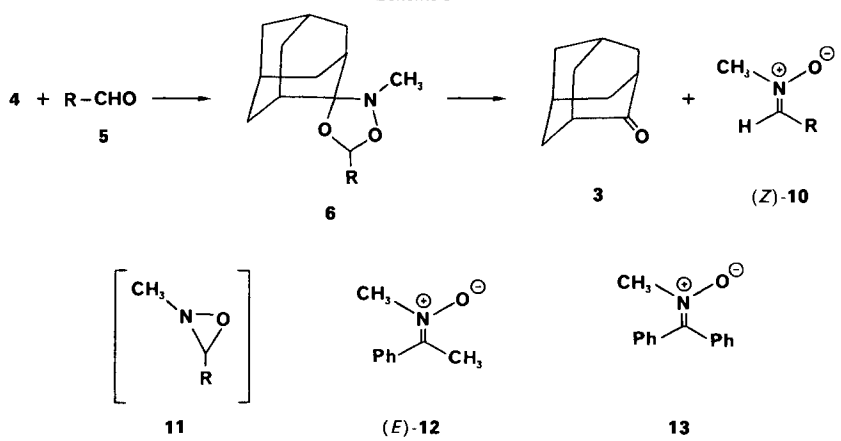
Search of the literature had provided some evidence that such a 1,3-dipolar cycloaddition is possible. Thus, in a previous communication, *De Carlo* and *Brandi* [10] reported the formation of 3,5-di(*tert*-butyl)-2-phenyl-1,4,2-dioxazolidine (**9**) on reacting of pivalaldehyde (**7**) and *N*-phenylhydroxylamine. The intermediate nitrone derivative **8** was also isolated and characterized.

Scheme 2



Chemistry. – First, we attempted the synthesis of the phenyl analogue **6** (R = Ph) starting with nitrone **4** and benzaldehyde (**5**; R = Ph). However, the reaction mixture did not contain any of the desired products. Instead, adamantan-2-one (**3**) was recovered along with a new nitrone derivative (*Z*)-**10** (R = Ph; *Scheme 3*). The formation of (*Z*)-**10** could be rationalized as arising from the fragmentation of an initially formed 1,4,2-dioxazolidine **6** to **3** and an oxaziridine intermediate **11**, which then rearranges to (*Z*)-**10**. The rearrangement of oxaziridines to the corresponding nitrones is extensively documented [16][17]. The configuration of aldonitrones of type **10** was previously [16] established as *Z*.

Scheme 3



The reaction **4** + **5** (R = Ph)→(*Z*)-**10** (R = Ph) represents a novel cycloaddition/rearrangement of nitrones. Other benzaldehydes **5** were also utilized in order to determine the general applicability of this transformation. They gave the corresponding (*Z*)-**10** in excellent yields (see the *Table, Entries 2* and *3*). The reaction of **4** with aliphatic aldehydes **5** to (*Z*)-**10** was quantitative with butyraldehyde and pivalaldehyde (*Entries 4* and *5*) but less satisfactory with heptanal (only 26% yield, *Entry 6*). Two solvents, toluene and THF were used to carry out this nitrone conversion. While, in the case of benzaldehyde, the yield of (*Z*)-**10** (R = Ph) was quantitative for both solvents, THF had the advantage over

Table. *Cycloaddition/Rearrangement on Reaction of Nitrones with Aldehydes*

Entry	Nitrone	R in **5**	Solvent (procedure)	M.p. of (*Z*)-**10** (solvent)	Yield [%] of (*Z*)-**10**
1	**4**	Ph	Toluene (*A*), THF (*B*)	84–85° (Et_2O/petroleum ether) [11]	98
2	**4**	4-NO_2–C_6H_4	Toluene (*A*)	211–212° (Et_2O/petroleum ether) [12]	89
3	**4**	4-CH_3O–C_6H_4	Toluene (*A*)	69–69.5° (Et_2O/petroleum ether) [11]	76
4	**4**	Pr	THF (*B*)	Oil [13][a]	100
5	**4**	$(CH_3)_3C$	THF (*B*)	Oil [14][b]	100
6	**4**	C_6H_{13}	Toluene (*A*)	Oil [15]	26
7	(*E*)-**12**	Ph	Toluene (*A*)	84–85° (Et_2O/petroleum ether) [11]	< 5
8	**13**	Ph	THF (*B*)	No reaction	

[a]) ^{1}H-NMR (200 MHz, $CDCl_3$): 0.87 (*t*, *J* = 7.7, 3H, Pr); 1.32–1.46 (*m*, 2H, Pr); 2.49–2.58 (*m*, 2H, Pr); 3.55 (*s*, CH_3N); 6.61 (*t*, *J* = 6.1, CH_2–C*H*=N).

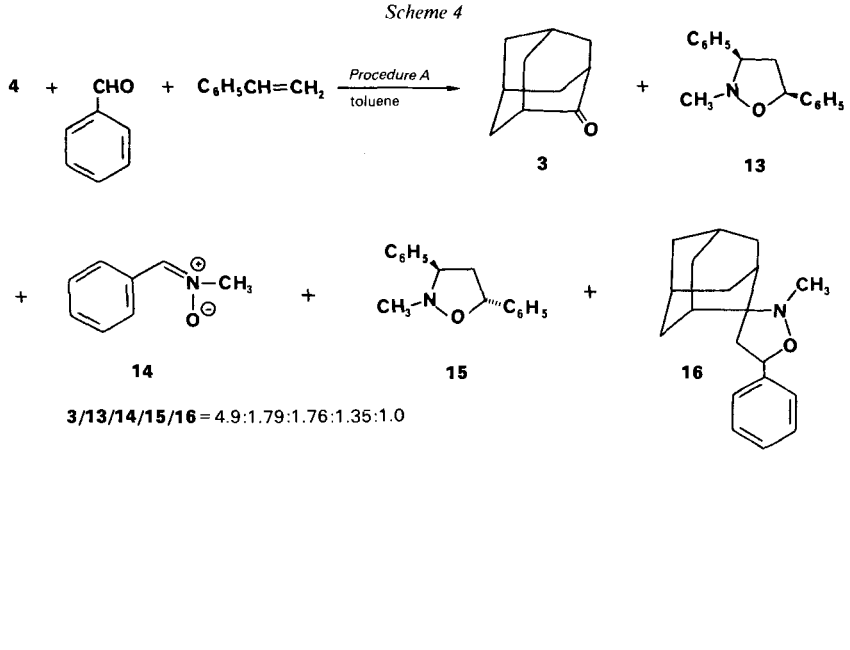
[b]) ^{1}H-NMR (200 MHz, $CDCl_3$): 1.20 (*s*, CH_3); 3.66 (*s*, CH_3N); 6.42 (*s*, C–C*H*=N).

toluene of providing less rigorous conditions and shorter reaction times. Thus, in the reaction with heptanal, where toluene was the solvent, the lower yield might be the result of the higher temperature and prolonged reaction time necessary to complete the reaction (24 h).

Reaction of the α-substituted nitrone (*E*)-**12** in place of **4** with benzaldehyde afforded the corresponding (*Z*)-**10** (R = Ph) in less than 5% yield *(Entry 7)*. Nitrone **13**, which was prepared from benzophenone and *N*-methylhydroxylamine, failed to react with benzaldehyde in THF at reflux.

It was further of interest to determine, whether the above nitrone conversion will take precedence in the presence of a competing functionality such as styrene. Thus, nitrone **4** was reacted with equimolar amounts of benzaldehyde and styrene *(Scheme 4)*. ^{1}H-NMR and HPLC analyses of the crude reaction mixture revealed the relative product ratio

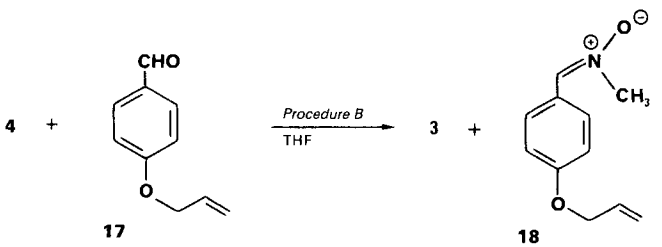
Scheme 4



adamantan-2-one (**3**)/*cis*-2-methyl-3,5-diphenylisoxazolidine (**13**)/*N*-benzylidenemethylamine *N*-oxide (**14**)/*trans*-2-methyl-3,5-diphenylisoxazolidine (**15**)/2-methyl-5-phenylspiro[isoxazolidine-3,2′-tricyclo[3.3.1.1^{3,7}]decane] (**16**) of 4.9 : 1.79 : 1.76 : 1.35 : 1.0. Hence, 83% of the products derived from the reaction of **4** with benzaldehyde and 17% from that of **4** with styrene *(Scheme 4)*. These results indicate the ability of benzaldehyde to favorably compete with other dipolarophiles in the 1,3-dipolar cycloaddition reaction of **4**.

Another competition experiment involving 4-[(prop-2-enyl)oxy]benzaldehyde (**17**; slight excess), which contains both competing functionalities and **4**, yielded, after reflux in THF for 21 h, **3** and *N*-{{4-[(prop-2-enyl)oxy]phenyl}methylidene}methylamine *N*-oxide (**18**) in a 1 : 1 ratio (by 200-MHz ^{1}H-NMR), besides unreacted **17** *(Scheme 5)*. Hence, of the two competing functionalities, the aldehyde group reacted exclusively with **4** under the reaction conditions.

Scheme 5



Experimental Part

General. M.p.: *Thomas-Hoover* capillary melting-point apparatus; uncorrected. IR Spectra (KBr): *Nicolet-MX-1-FT* spectrometer. ^{1}H-NMR spectra: *Varian-EM-360-A* (60 MHz) spectrometer; TMS as internal standard (= 0 ppm); *Bruker-IBM 200 SY Fourier* transform (200 MHz) with the same internal standard. All spectra were consistent with the assigned structures.

Nitrone Cycloaddition/Rearrangement. Procedure A. Under N_2, a soln. of 1.75 g (9.84 mmol) of **4** and 1.0 ml (9.84 mmol) of benzaldehyde (**5**; R = Ph) in 50 ml of toluene was heated to reflux and stirred for 26 h (TLC monitoring (silica gel *60* F_{254}, 5 × 10 cm, 0.25 mm; $CHCl_3$/MeOH 9 : 1): complete conversion). The mixture was cooled to r.t., then diluted with 100 ml of Et_2O and extracted with H_2O (4 × 50 ml). The org. layer was dried ($MgSO_4$) and evaporated: 0.39 g of **3** after crystallization from Et_2O. The aq. layer was basified with K_2CO_3 and extracted with $CHCl_3$ (4 × 50 ml). The org. layer was dried ($MgSO_4$) and concentrated. Crystallization from Et_2O/petroleum ether 4 : 1 yielded 0.82 g (62%) of *N-[(Z)-benzylidene]methylamine N-oxide* ((*Z*)-**10**; R = Ph). M.p. 81–83°. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.88 (*s*, CH_3N); 7.37 (*s*, CH=NO); 7.41–7.44 (*m*, 3 arom. H); 8.18–8.23 (*m*, 2 arom. H).

Procedure B. Under N_2, a soln. of 1.75 g (9.84 mmol) of **4** and 1.05 ml (10.3 mmol) of benzaldehyde (**5**; R = Ph) in 50 ml of THF was heated to reflux and stirred for 5.5 h. TLC (see above) indicated complete conversion to **4** and (*Z*)-**10** (R = Ph). The mixture was cooled to r.t. and evaporated. ^{1}H-NMR: 100% conversion to **4** and (*Z*)-**10** (R = Ph).

(*Z*)-**10** (R = Ph) was also prepared by an alternative route according to [18] and found to be identical in every respect with the product obtained above.

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