A New Acylative Cycloaddition Reaction

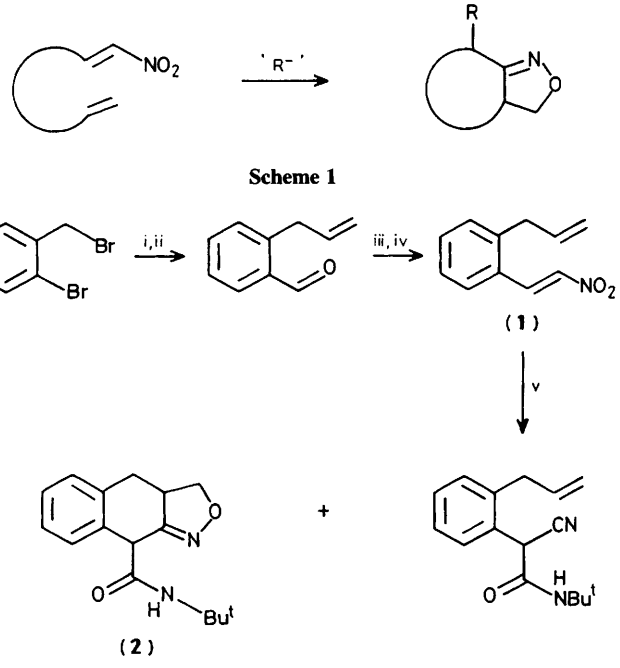
John Knight and Philip J. Parsons

Department of Chemistry, University of Southampton, Southampton SO9 5NH, U.K.

A new procedure for the intramolecular nitrile oxide cycloaddition is described; the procedure involves the generation of a nitrile oxide resulting from the conjugate addition of an isocyanide to a nitroalkene, and subsequent trapping with an alkene.

The nitrile oxide cycloaddition reaction is widely used in synthesis,[1—3] because useful functionality and stereochemistry can be produced in one step.[4,5] In the course of our work on the intramolecular nitrile oxide cycloaddition (INOC) reaction we required a method for introducing functionality at a position α to an isoxazoline. We wondered if the new functionality could be introduced by conjugate addition to a nitroalkene at the same time as resulting in cycloaddition (Scheme 1).

As earlier work by Foucard[6] and Saegusa[7] indicated that isonitriles can add to nitroalkenes, we made the nitroalkene (**1**), but it failed to react with phenyl isocyanide. When the reaction was repeated using the more nucleophilic t-butyl isonitrile, the desired cyclisation occurred (Scheme 2).



Scheme 1

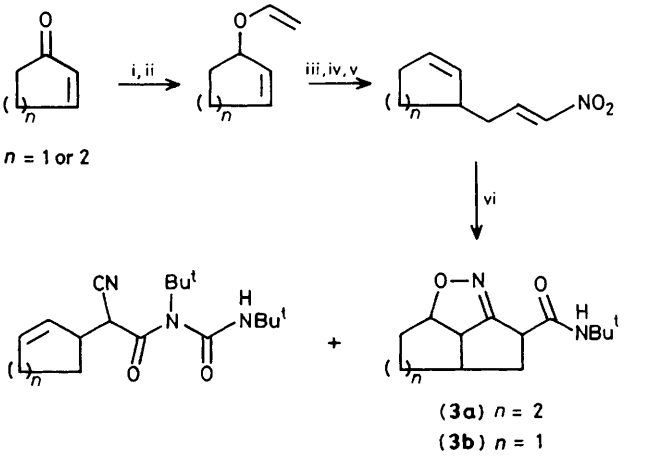
Scheme 2. *Reagents:* i, CH_2=CHBr, Mg, CuI, 2,2'-dipyridyl, tetrahydrofuran (THF), PhH; ii, Mg, dimethylformamide (DMF), THF, 0 °C; iii, $MeNO_2$, KOH–MeOH, pH 8, followed by H_2SO_4 to pH 4; iv, $MeSO_2Cl$, Et_3N, CH_2Cl_2; v, Bu^tNC, MeCN, 80 °C.

Table 1. Yields and stereochemistry of the cycloaddition products.

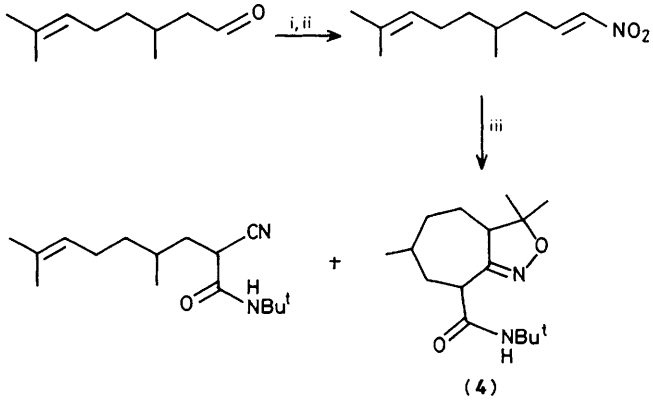
Compound	Yield/%	Stereochemistry
(**2**)	48	2 : 1 mixtures
(**3a**)	88	1 : 1 : 1 : 1 mixture of diastereoisomers
(**3b**)	36	single diastereoisomer
(**4**)	14	1 : 1 mixture of diastereoisomers

Thus, when an 0.5 M solution of (**1**) in dry acetonitrile was stirred with 1.2 equiv. of t-butyl isocyanide at 80 °C for 66 h, we obtained the desired tricyclic product (**2**) in 48% yield as a 2 : 1 mixture of diastereoisomers.†‡ Further applications of this new cyclisation are shown in Schemes 3 and 4.

The yields of the cycloaddition products are shown in Table 1.



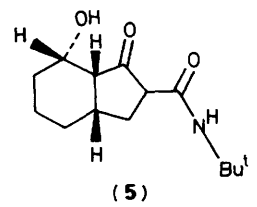
Scheme 3. *Reagents:* i, $NaBH_4$, Ce^{III}, MeOH; ii, $EtOCH{=}CH_2$, $Hg(OAc)_2$; iii, 190 °C, 2 h; iv, $MeNO_2$, KOH–MeOH, pH 8, followed by H_2SO_4, pH 4; v, $MeSO_2$, Cl, Et_3N, CH_2Cl_2; vi, Bu^tNC, MeCN, 80 °C.



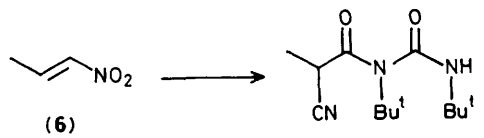
Scheme 4. *Reagents:* i, $MeNO_2$, KOH–MeOH, pH 8, followed by H_2SO_4, pH 4; ii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; iii, Bu^tNC, MeCN, 80 °C.

† All compounds are racemic, but for clarity only one isomer is depicted.

‡ All new compounds were characterised by ^1H n.m.r., i.r., mass spectral and/or microanalytical data.



(5)



(6) (7)

Scheme 5

When the diastereoisomeric mixture (**3a**) was stirred with Pd–C in aqueous ethanol–acetic acid in an atmosphere of hydrogen, the keto alcohol (**5**) was isolated as a single diastereoisomer in 85% yield.§ Initial studies on intermolecular cycloadditions with nitropropene (**6**) and alkenes have resulted in the isolation of acyl urea (**7**) with no observed cycloaddition.

In summary our new cycloaddition procedure is mild and generally efficient for the construction of polyfunctional rings.

We thank Dr. R. Southgate of Beecham Pharmaceuticals for his interest and John Tyler of Beechams for proton n.m.r. and nuclear Overhauser enhancement studies. The S.E.R.C. and Beecham Pharmaceuticals are gratefully acknowledged for a CASE award to J. K.

Received, 15th August 1986; Com. 1174

§ Confirmed by 2D (COSY-45) and nuclear Overhauser enhancement n.m.r. studies.

References

1 D. C. Lathbury and P. J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1982, 291.
2 T. Kametani, *Heterocycles*, 1982, **17**, 463.
3 A. P. Kozikowski and P-W. Yuen, *J. Chem. Soc., Chem. Commun.*, 1985, 847.
4 D. P. Curran, *J. Am. Chem. Soc.*, 1982, **104**, 4024; 1984, **106**, 1845.
5 T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339; G. A. Lee, *Synthesis*, 1982, 508.
6 A. Foucaud, C. Razorilalana-Rabearivony, E. Loukakou, and H. Persan, *J. Org. Chem.*, 1983, **48**, 3639.
7 T. Saegusa, S. Kobayashi, Y. Ito, and I. Marino, *Tetrahedron*, 1972, **28**, 3389.