

## Diels-Alder Cycloadditions of 1,2,4-Triazoline-3,5-diones with *N*-Substituted-1,2-dihydropyridines

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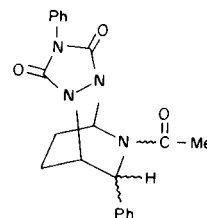
Sir:

Treatment of pyridines with organolithium reagents affords *N*-lithio-1,2-dihydropyridines (1) which were shown (2,3) to react with acyl halides at  $-65^\circ$  to yield *N*-acyl-1,2-dihydropyridines **1**. The facile ( $\pi_4 + \pi_2$ ) cycloaddition reaction of dienamines **1** with the highly reactive 1,2,4-triazoline-3,5-diones **2** now provides a quantitative route to the pharmacologically interesting 5,6-disubstituted-2,3,5-triazabicyclo[2,2,2]oct-7-ene-2,3-dicarboxylic acid imides **3**.

A typical reaction involves the dropwise addition of the dienamine **1a** (1 equivalent) in methylene chloride (10 ml.) to a solution of the 1,2,4-triazoline-3,5-dione (1 equivalent) **2a** in methylene chloride (20 ml.) at room temperature which results in discharge of the red color. Removal of the solvent *in vacuo* gives rise to 5-acetyl-6-phenyl-2,3,5-triazabicyclo[2,2,2]oct-7-ene-2,3-dicarboxylic acid *N*-phenylimide **3a**. Reduction of **3a** in methanol using 10% Palladium-charcoal for 2.5 hours with hydrogen at 30 psi afforded the reduced product **4** (85%) (4). The

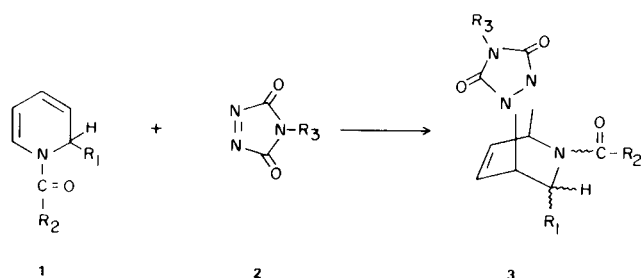
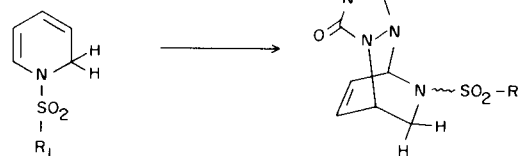
dienamine **1e** (5) which does not contain functionality at the 2-position reacts in a similar manner to yield **3e**: ir (potassium bromide): 1695, 1705, 1710, 1720  $\text{cm}^{-1}$  (C=O); nmr (chloroform):  $\delta$  7.36 (5H, m, Ph), 6.36-6.76 (3H, m, C<sub>4</sub>-H, C<sub>7</sub>-H, C<sub>8</sub>-H), 5.04 (1H, d ( $J_{1,7} = 5$  Hz) of d ( $J_{1,6} = 2.75$  Hz), C<sub>1</sub>-H), 3.8 (1H, d ( $J_{6,6^1 \text{ gem}} = 11$  Hz) of d ( $J_{1,6} = 2.75$  Hz), C<sub>6</sub>-H), 3.73 (3H, s, -OCH<sub>3</sub>), 3.17 (1H, d ( $J_{6,6^1 \text{ gem}} = 11$  Hz) of d ( $J_{1,6} = 2.75$  Hz), C<sub>6</sub>-H);  $M^+$  314.

Similarly, *N*-sulfonyl-1,2-dihydropyridines **5**, prepared by the reaction of pyridine and the appropriate sulfonyl chloride in the presence of sodium borohydride (6), react



4

with **2**. For example, reaction of *N*-methanesulfonyl-1,2-dihydropyridine **5a** with **2a** gave 5-methanesulfonyl-



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	3, m.p.
(a)	Ph	Me	Ph	181-183°
(b)	Ph	OEt	Ph	150-154°
(c)	Ph	Ph	Ph	202-204°
(d)	Ph	Me	Et	70°
(e)	H	OMe	Ph	152-156° dec.

	R <sub>1</sub>	R <sub>2</sub>	6, m.p.
(a)	Me	Ph	170-175° dec.
(b)	Ph	Ph	145°
(c)	Me	Et	

2,3,5-triazabicyclo[2,2,2]oct-7-ene-2,3-dicarboxylic acid *N*-phenylimide **6a** (100%): ir (potassium bromide): 1155, 1340  $\text{cm}^{-1}$  ( $\text{SO}_2$ ), 1725, 1795  $\text{cm}^{-1}$  (C=O); nmr (DMSO- $d_6$ ):  $\delta$  7.45 (5H, m, Ph), 6.6-6.96 (2H, m, C<sub>7</sub>-H, C<sub>8</sub>-H), 6.06 (1H, d ( $J_{4,8} = 6$  Hz) of d ( $J_{4,7} = 1.5$  Hz), C<sub>4</sub>-H), 5.2 (1H, m, C<sub>1</sub>-H), 3.81 (1H, d ( $J_{6,6^1}$  gem = 10.5) of d ( $J_{1,6} = 3$ ), C<sub>6</sub>-H), 3.24 (1H, d ( $J_{6,6^1}$  gem = 10.5) of d ( $J_{1,6} = 3$ ), C<sub>6</sub><sup>1</sup>-H), 3.08 (3H, s, -SO<sub>2</sub>CH<sub>3</sub>); M<sup>+</sup> 334.

In reactions of dienes with **2a** stereoisomerism is not present about the bridge nitrogens in the adducts due to the planar structure of the urazole ring (7,8). A variable-temperature nmr study (-65 to +31°) including reaction at -65° of **3a** showed no temperature dependence which indicates that bonding about the bridgehead nitrogens in **3** is planar or close to planar (9).

Since other *N*-substituted-1,2-dihydropyridines **1** can be prepared (2,3) the above reaction should allow the synthesis of a variety of adducts **3** with a wide selection of substituents at the 5-, 6- and *N*-imide positions.

The reactions of **1** with other dienophiles, the stereo-

chemistry of the adducts and the biological screening of compounds **3** are presently under study (10).

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- (9) Reactions of **1** with dienophiles capable of producing adducts possessing stereochemistry at the bridgehead positions *e.g.*, *N*-phenylmaleimide) are now in progress.
- (10) This work was supported by a Medical Research Council of Canada grant (MA-4888) for which we are grateful.