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INTRAMOLECULAR DIELS-ALDER REACTIONS OF ISOQUINOLINE-1-CARBOXAMIDES

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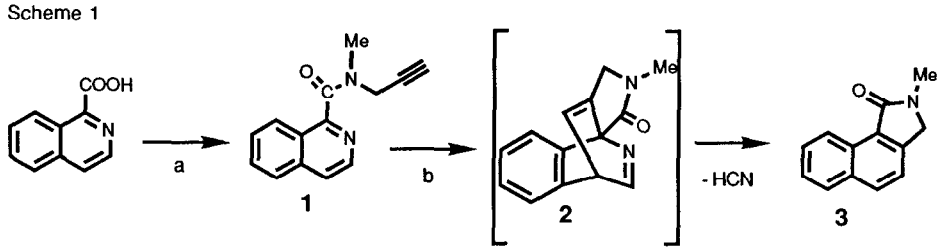
Abstract *N*-methyl-*N*-propargyl and *N*-methyl-*N*-allylisoquinoline-1-carboxamides undergo facile intramolecular Diels-Alder reactions to give fused *N*-methyl-γ-lactams.

Inverse electron demand Diels-Alder reactions between electron deficient heterocyclic azadienes and electron-rich dienophiles are well known.[2] The ease with which these reactions occur is further enhanced when carried out in an intramolecular fashion.[3,4] Numerous examples of reactions of unactivated dienophiles tethered via an ether, thioether or amine linkage to tetrazines,[5] triazines,[3,4,6] pyridazines,[7] pyrazines[8] and pyrimidines[9] have shown the versatility of this reaction for the synthesis of novel bicyclic fused ring heterocycles More recently, examples of alkyl tethers to pyrimidines[10a], nitropyridines[9b] and pyrazines[11] have also been reported.

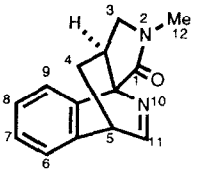
In the course of an investigation of the scope of the intramolecular Diels-Alder reaction with various nitrogen heterocycles linked to alkynes or olefins *via* an amide, we have explored the thermal cyclizations of *N*-alkyl-*N*-propargyl or *N*-alkyl-*N*-allylisoquinoline-1-carboxamides. Conversion of isoquinoline-1-carboxylic acid into the corresponding amide by treatment of its acid chloride with *N*-methylpropargyl amine gives **1**[12] which undergoes cycloaddition in refluxing anhydrous xylene to give the lactam, **3**[13] as shown in Scheme 1. In analogy to a previous proposal,[9a] this product undoubtedly arises from elimination of hydrogen cyanide from the intermediate adduct, **2**, *via* a retrograde Diels-Alder reaction, although we were also unable to isolate **2**

Scheme 1



(a) (i) oxalyl chloride, (ii) *N*-methylallylamine, TEA, (b) reflux (xylenes)

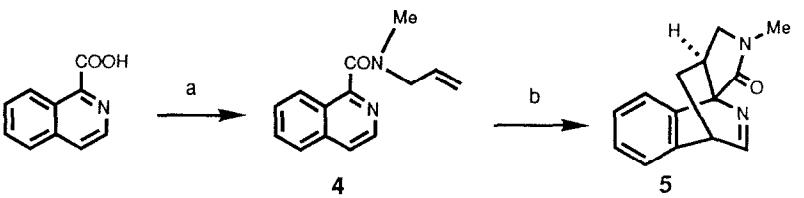
Table 1 ^{13}C-NMR and ^{1}H-NMR Data on Cycloadduct **5**



Position	^{13}C	^{1}H
4	25 33	1 40 (1H,dd) 1 78 (1H,m)
12	30 12	3 01 (3H,s)
3a	40 06	2 18 (1H,m)
5	43 39	4 22 (1H,m)
3	52 75	3 02 (1H, app t, J~9 7Hz) 3 31 (1H,dd, Jgem=9 2Hz, Jvic=7 3Hz)
9b	70 45	–
9	121 32	7 89 (1H,m)
6	124 34	7 24 (3H,m)
7	126 28	
8	126 58	
9a	135 06	–
5a	140.33	–
1	172 47	–
11	173 72	8 64 (1H,d)

If, however, the *N*-methyl-*N*-allylamide, **4**,[14] is substituted for **1** in the above sequence, the resulting cycloaddition in refluxing xylene yields adduct **5** (see Scheme 2) which cannot aromatize via retrograde Diels-Alder reaction and can therefore be isolated and characterized Lactam **5** is obtained as a crystalline solid[15] on cooling of the reaction mixture. The proposed structure was confirmed by proton and carbon-13 NMR as shown in Table 1 The only diastereomer that could be detected in this reaction was shown by single crystal *X*-ray analysis[16] to have the relative stereochemistry depicted below

Scheme 2



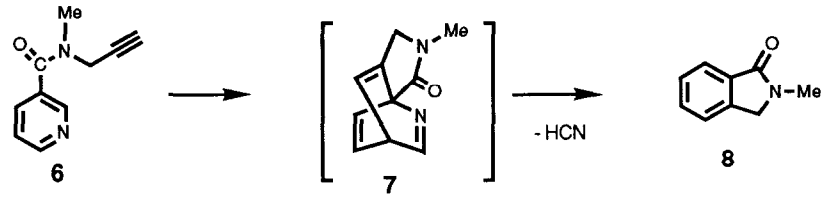
a (1) CDI, DMF, (2) *N*-methylallylamine, b reflux (xylenes)

It is well established that the relative ease of intramolecular aza-Diels-Alder reactions is dependent on the presence of a suitably electron-deficient azadiene component,[5e,8a,b, 10b] and is

also sensitive to steric and conformational effects which affect orbital overlap.[9] The only previous report of intramolecular Diels-Alder cyclizations involving an isoquinoline ring system is a report by Gisby et al.[17] in which 3-methyl-2-pent-4-enylisoquinolinium bromide and 2,3-dimethyl-4-pent-4-enylisoquinolinium iodide were thermolyzed to give cycloadducts similar in structure to **5.** Although these cyclizations occurred at comparable temperature (145°C in CH_3CN), the more closely analogous 2-methyl-1-pent-4-enylisoquinolinium iodide could not be cyclized. In the present example, the combination of delocalization of electron density over the extended isoquinoline aromatic system and the use of an amide linkage as the point of attachment for the dienophile side chain to the azadiene gives a sufficiently electron deficient diene to allow cycloaddition to occur at moderate temperature. The *N*-methylamide tether provides adequate conformational constraint to eliminate the need for the geminal substitution at the α-carbon. Hence, the starting materials are more readily accessible, and the potential synthetic utility of the products obtained is greater. The *N*-methyl group of the amide has also been replaced with other alkyl groups (*i.e.*, benzyl or phenethyl) without any deleterious effect on the rate or yield of cycloadduct.

Previously reported intramolecular cycloaddition reactions of 2-(alkynyl)pyridines occur at higher temperature and have required at least one nitro substituent on the pyridine nucleus,[9] and in addition have utilized the Thorpe-Ingold (*gem*-dimethyl)[18] effect to facilitate the reaction. Another recent example of cyclization of an *N*-benzyl-*N*-acyl-3-aminopyridine system has also been reported.[19] We have also examined the cycloaddition in the pyridine series, and have successfully cyclized *N*-methyl-*N*-propargylpyridine-3-carboxamide (toluene, sealed tube, 200°C) to the expected 1,2-dihydro-2-methylisoindol-3-one (Scheme 3)

Scheme 3



The corresponding pyridine-4-carboxamide analog, however, gave no intramolecular Diels-Alder products under similar reaction conditions.

Acknowledgements: We acknowledge the staff of Analytical Sciences in Central Research & Development for spectral measurements as well as Drs George A Boswell and E Ciganek for helpful discussions The technical assistance of Mr James C Bonavita is also gratefully acknowledged

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[12]**1:** mp 84-86°C (EtOAc/hexanes). IR (nujol): 3300, 1640, 820, 750 cm^{-1}. UV (CH_3CN) 325 (4290) 317 (3180) 308 (3340) 295 (2090) 272 (5140) 217 (51,600) nm. NMR (200 MHz, DMSO-d_6): δ 2.82 and 3.27 (unequal singlets, 3H, N-CH_3) 3.38 (1H, t, J=2.5Hz, =CH), 4.03 and 4.57 (unequal doublets, J=2.5Hz, 2H, N-CH_2) 7.7-8.2 (5H, m), 8.58 (1H,d, J=6Hz, H-3). Mass spectrum: m/z 224.0957 (P; Calcd. for $C_{14}H_{12}ON_2$: 224.0949), 167 (P-C_2H_3ON) 129 (P-C_5H_6ON). Anal. calcd. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.14; H, 5.64; N, 12.52.

[13]**3:** mp 128-130°C ($CHCl_3$/petroleum ether). IR (nujol) 1685, 820, 795 cm^{-1}. UV (CH_3CN) 322 (1720) 307 sh (5440) 296 (8500) 288 sh (7410) 225 (52,200) nm. NMR (200 MHz, $CDCl_3$) δ 3.12 (3H,s) 4.18 (2H,s) 7.2-8.0 (5H,m) 9.26 (1H, dd, J=2.5, 8 Hz; H peri to C=O). Mass spectrum m/z 197.0848 (P; Calcd. for $C_{13}H_{11}ON$: 197.0840) 168 (P-CHO) 139 (P-C_2H_4ON). Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.99; H, 5.57; N, 6.89.

[14]**4:** IR (nujol) 1630 cm^{-1}. UV (CH_3CN) 325 (4290) 317 (3180) 308 (3340) 295 (2090) 272 (5140) 217 (51,600). NMR (300 MHz, $CDCl_3$, mix of CO-N rotamers) δ 2.80 and 3.16 (singlets, 3H, N-CH_3) 3.74 and 4.22 (doublets, 2H, N-CH_2) 5.10 and 5.35 (multiplets, 2H, =CH_2) 5.69 and 5.99 (multiplets, CH=) 7.57-7.75 (m, 3H) 7.85 (1H,m) 8.03 (d, 1H) 8.53 (t, 1H)

[15]**5:** IR (nujol) 1700 (C=O) 1615 (C=N) cm^{-1}. Mass spectrum m/z 226.1088 (P; Calcd. for $C_{14}H_{14}ON_2$, 226.2005) 199 (P-HCN) 142 (P-HCN-C_2H_3ON) 128 (P-HCN-C_3H_5ON). Anal. calcd. for $C_{14}H_{14}ON_2$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.30; H, 6.18; N, 12.34.

[16] *X*-ray cyrstallographic data was collected on an Enraf-Nonius CAD4 diffractometer using MoKα radiation. The structure was solved by direct methods (MULTAN) and refined by least squares analyses. The crystal used for analysis (CH_2Cl_2/cyclohexane) was monoclinic, $P2_1/c$(No. 14), a=5.967(4), b=8.087(1), c=23.420(10) Å, Z=4, D_c=1.33g/cc; R=0.047 for 1696 reflections [$I \geq 3.0\sigma(I)$].

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