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Diels-Alder reactions of *N*-tosyl-3-nitroindole and dienamides: synthesis of intermediates of *Aspidospermine* alkaloids

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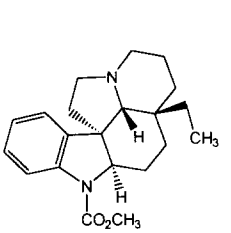
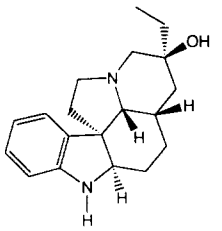
Abstract: *N*-tosyl-3-nitroindole undergoes high yielding Diels-Alder reactions with 1-(*N*-acyl-*N*-alkylamino)-1,3-butadienes in a regioselective manner, to afford advanced intermediates for the synthesis of *Aspidospermine* alkaloids. © 1999 Elsevier Science Ltd. All rights reserved.

The Diels-Alder (D-A) reaction is one of the most useful reactions in preparative organic chemistry.[1] Its potential in heterocyclic chemistry and natural product synthesis is well known.[2] As the following discussion illustrates, the employment of *N*-tosyl-3-nitroindole in Diels-Alder reactions with appropriate dienamides allow us to approach regioselectively useful intermediates in the synthesis of natural products (e.g. *Aspidospermine* Alkaloids, Scheme 1).

Scheme 1



(-) - ASPIDOSPERMINE



(+) - PANDOLINE

In this connection, we have examined the possibility of making use of heteroatom-substituted dienes, which would provide the appropriate functionality array in addition to enhanced reactivity. General synthetic utility in Diels-Alder reactions of 1-(*N*-acyl-*N*-alkylamino)-1,3-butadienes has been well demonstrated. [3] A most significant feature contributing to the considerable synthesis applications of these dienes is their potential high regio- and stereoselectivity in cycloaddition reactions with unsymmetrical, and often unreactive, dienophiles, like the previously cited nitroindole, providing access to a variety of amino-functionalized cyclic systems.

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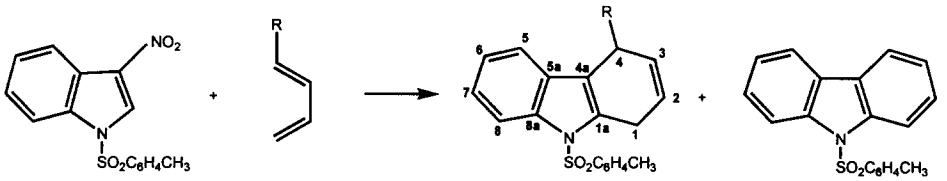
Considering the higher reactivity and thermal instability[4] of the 1-(*N*-acyl-*N*-alkylamino)-dienes compared to isoprene, milder reaction conditions were chosen. Thus, heating a 1:2 molar mixture of nitroindole[5] **1** and 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene[6] **2a** at 90°C for 4 days[7] afforded a single 1:1 regioisomeric adduct 4-(*N*-acetyl-*N*-propylamino)-*N*-tosyl-dihydrocarbazole[8] **3a** (with thermal extrusion of nitrous acid accompanying the D-A reaction) and the unexpected *N*-tosyl-carbazole[9] **4** in a ca. 3:1 ratio and 65% yield, recovering unreacted dienophile (ca. 30%) and diene (Scheme 2). Under the same reaction conditions, the 1-(*N*-benzoyl-*N*-bencylamino)-1,3-butadiene[6] **2b** exposed to **1** behaved like its *N*-acetyl-*N*-propylamino-substituted analogue, yielding a 2:1 mixture (ca. 70% yield) of the adduct[10] **3b** and **4**. Lowering the reaction time to 1 day led in both cases to a 4:1 product mixture in ca. 20 % yield and longer reaction times (7 days) slightly increased the yields but the product ratio changed to ca.1:5. (see Table 1).[11]

Scheme 2



1 **2a** R = *N*-acetyl-*N*-propylamino **2b** R = *N*-benzoyl-*N*-bencylamino **3a** R = *N*-acetyl-*N*-propylamino **3b** R = *N*-benzoyl-*N*-bencylamino **4**

In order to explore the reaction pathway, the named reactions were carried out under different experimental conditions (see Table 1). By increasing the reaction temperature to 160°C (3 h) the product ratio was 1:6 and at 24 h the respective 4-substituted-*N*-tosyl-dihydrocarbazoles **3a** and **3b** were not detected, obtaining the highest *N*-tosyl-carbazole yield (ca. 85%). At 200°C, presumably because of appreciable diene decomposition, *N*-tosyl-carbazole **4** was obtained only in 52% (heating at this temperature during 72 h caused the detosylation of the obtained *N*-tosyl-carbazole).[12]

Table 1

Dienophile	Diene	Temperature	Time	Product	Product ratio, yield[a]
1	**2a**	90°C	4 d	**3a ; 4**	3:1, 65%
		90°C	1 d	**3a ; 4**	4:1, 20%
		90°C	7 d	**3a ; 4**	1:5, 66%
		160°C	24 h	**4**	85%
		160°C	3 h	**3a ; 4**	1:7, 77%
		200°C	24 h	**4**	55%
		200°C	72 h	**4 + carbazole**	ca. 52%
	2b	90°C	4 d	**3b ; 4**	5:2, 76%
		90°C	1d	**3b ; 4**	3:1, 25%
		90°C	7 d	**3b ; 4**	1:4, 68%
		160°C	1 d	**4**	80%

[a] based on starting indole

The results of this type of D-A reactions involving the *N*-tosyl-3-nitroindole indicate a possible sequential pathway where the ease of thermal extrusion of nitrous acid accompanying the D-A reaction would lead to the 4-substituted-*N*-

tosyl-dihydrocarbazole adduct, which would undergo thermal aromatization by losing the *N*-acyl-*N*-alkylamino substituent. This specific diene-dienophile combination reveals good yields, extraordinary regioselectivity, with regiocontrol being completely dominated by the acylamino substituent in the diene and the powerful electron withdrawing nitro group in the dienophile.[13]

In conclusion, we report here the utility of this special Diels-Alder reaction involving a heteroaromatic dienophile for the construction of the C ring of the above named alkaloid skeleton by [4+2]π cycloaddition. Moreover the use of 1-(*N*-acyl-*N*-alkylamino)-1,3-butadienes permits the attainment of the appropriate functionality for continuing the synthesis of the cited alkaloid. Complementary, the employment of appropriate 2- and/or 3-substituted 1-(*N*-acyl-*N*-alkylamino)-1,3-butadienes points the way to a new route of synthesis of substituted carbazoles.

Acknowledgments. We are indebted to Universidad Nacional del Litoral (UNL), República Argentina. This work received financial support from the Science and Technology Secretariat – UNL – CAI+D Program (Projects 94-0858-007-056 and 96-00-024-161). We thank Dr. Gonzalez Sierra from the IQUIOS-Universidad Nacional de Rosario (Santa Fe, Argentina) for the NMR experiments. We thank JICA (Japan International Cooperation Agency) the donation of a FTIR – Model 8000 – SHIMADZU to the CENACA (Centro Nacional de Catálisis, Santa Fe, Argentina).

References and Notes

[1] O. Diels, K. Alder, *Liebigs Ann. Chem.* **1928**, *460*, 98.

[2] Wenkert showed for the first time that indoles can act as dienophiles in D-A reactions with simple nucleophilic dienes, when 3-substituted with electron-withdrawing groups and *N*-substituted with a powerful electron-withdrawing function. In order to attain good yields, these cycloaddition reactions have to be performed under high temperatures (over 150°C), showing poor regioselectivity. E. Wenkert, P. Moeller, S. Piettre, *J. Am. Chem. Soc.* **1988**, *110*, 7188-7194.

[3] W. Oppolzer, L. Bieber, E. Francotte, *Tetrahedron Lett.* **1979**, 4537-4540.

[4] W. Oppolzer, W. Frostl, *Helv. Chim. Acta* **1975**, *58*, 587-589.

[5] The synthesis of N-tosyl-3-nitrondole was performed starting from N-tosylindole[2] following a procedure proposed by H. Anderson, C. Loader, R. X. Xu, N. Le, N. Gogan, R. McDonald, L. Edwards, *Can. J. Chem.* **1985**, *63*, 896-902 for the synthesis of 3-nitro-1-(phenylsulfonyl)-pyrrole, with some modifications: A mixture of 70% nitric acid (4.15 ml) and acetic anhydride (60 ml), cooled under –10°C is added dropwise over a 30 min period to a stirred mixture of N-tosylindole (19.56 mmol) and acetic anhydride (60 ml). The mixture was stirred for further 2 h, let warm to room temperature and the poured onto crushed ice. The aqueous mixture was extracted with methylene chloride, the organic layers combined were washed twice with water, dried with Na_2SO_4, and then the solvent removed. The yellow residue was crystallized twice with absolute ethanol to give pale yellow needles in 41% yield, m.p.168-169°C, **IR** (KBr): 1543, 1491, 1383, 1176, **^{1}H-RMN** ($CDCl_3$, 200 MHz): 2.4 (s, 1H, Me_{tosyl}), 7.32 (d, 2, *o*-Hs_{tosyl}, J = 8 Hz), 7.45 (m, 2H, H_5 + H_6), 7.67 (d, 2H, *m*-Hs_{tosyl}, J = 8Hz), 7.99 (m, 1H, H_4), 8.24, (d, 1H, H_7, $J_{6\text{-}7}$= 10 Hz), 8.56 (s, 1H, H_2).

[6]Following the procedure proposed by W. Oppolzer, L. Bieber, E. Francotte, *Tetrahedrom Lett.* **1979**, 981-984, without isolation of the imine intermediate, and purification by rapid chromatography (in either silica gel or alumina,

hexane/ethyl acetate) the 1-(N-acetyl-N-propylamino)-1,3-butadiene **2a** was obtained as a yellow oil, 50% overall yield, **IR** (neat): 1638, 1678 cm^{-1}; **^{1}H-NMR** (CCl_4, 60 MHz): 0.95, (t, 3H, CH_2-CH_2-$C\underline{H}_3$, *J*=7Hz), 1.65 (m, 2H, CH_2-$C\underline{H}_2$-CH_3), 2.14 (s, 3H, Me), 3.51 (t, 3H, $C\underline{H}_2$-CH_2-CH_3, *J*= 7Hz), 4.8-6.9 (m, 5H, H_2C=CH-CH=); 7.3 (d, 1H, CH=C$\underline{H}$-N-, *J*= 8 Hz). The diene **2b** was obtained following the same procedure.

[7] **General procedure for thermal D-A reactions:** an ampoule containing 0.5 mmol of the dienophile, 1.5 mmol of diene in 0.5 ml of benzene was cooled in liquid nitrogen, sealed and then heated in a silicon bath at the required temperature and time. It was then cooled once more in liquid nitrogen, opened, evaporated and the residue chromatographed (silica gel, hexane/ethyl acetate).

[8] Pale yellow plates (recrystallized from hexane-chloroform), m.p. 115-115.5°C, **IR** (KBr): 1677, 1602, 1373, 1176. **^{1}H-NMR** ($CDCl_3$, 200 MHz): 0.5 (t, 3H, -CH_2-CH_2-$C\underline{H}_3$, *J* = 7.05 Hz) , 0.87 (m, 2H, -CH_2-$C\underline{H}_2$-CH_3), 2.15 (s, 1H, Me-acyl) 2.32 (s, 1H, M2-tosyl), 2.75 (m, 2H, -$C\underline{H}_2$-CH_2-CH_3), 3.71 (m, 2H, Hs_1), 5.73 (dm, 1H, H_3, $J_{2\text{-}3}$= 10 Hz), 6.16 (dm, 1H, H_2, $J_{3\text{-}2}$= 10 Hz), 6.66 (md, 1H, H_4, $J_{3\text{-}4}$= 6 Hz), 7.17 (d, 2H, *orto*-Hs, *J* = 8.5, 1.5), 7.23-7.41 (m, 3H, H_5, H_6, H_7), 7.63 (dt, 2H, *meta*-Hs, *J* = 8.5, 1.5 Hz) 8.16 (d, 1H, H_8, *J* = 8.22 Hz). **^{13}C-NMR** ($CDCl_3$, 200 MHz):11.36 (CH_2-CH_2-$C\underline{H}_3$), 21.37 (Me-tosyl), 21.64 (Me-acetyl), 23.70 (CH_2-$C\underline{H}_2$-CH_3), 26.14 (C_1), 46.03 ($C\underline{H}_2$-CH_2-CH_3), 46.23 (C_4), 114.18 (C_8), 116.19 (C_{4a}), 119.45 (C_5), 123.8 (C_7), 124.59 (C_6), 125.36 (C_3), 126.11 (*orto*-C), 126.43 (C_2), 128.35 (C_{5a}), 129.81 (*meta*-C), 134.9 (*ipso*-C), 135.84 (C_{1a}), 136.07 (C_{8a}), 144.82 (*para*-C), 170.80 (C=O). Relative configuration at C-4 position in **3a** was determined by NOESY correlations between acetyl protons (δ = 2.15) and H_4 (δ_H 6.66) and H_3 (δ_H 5.73), and between -$C\underline{H}_2$-CH_2-CH_3 (δ_H 2.75) and H_5 (δ_H 7.23-7.41).

[9] **^{1}H-NMR** ($CDCl_3$, 200 MHz): 2.15 (s, 3H, $CH_{3\ tosyl}$), 6.99 (dt, 2H, *m*-$Hs_{\text{-tosyl}}$, *J*= 8.2, 1.8 Hz), 7.31 (td, 2H, $H_{3,6}$, *J* = 7.6, 7.6, 0.9 Hz), 7.45 (ddd, 2H, $H_{2,7}$, *J* = 8.5, 7.6, 0.6 Hz), 7.65 (dt, 2H, *o*-$Hs_{\text{-tosyl}}$, *J* = 8.2, 1.8 Hz), 7.84 (ddd, 2H, $H_{4,5}$, *J* = 7.6, 1.5, 0.6 Hz), 8.32 (dt, 2H, $H_{1,8}$, *J* = 8.5, 0.9, 0.6 Hz);**^{13}C-NMR** ($CDCl_3$, 200 MHz): 21.3 (Me); 115 (C_1+C_8); 119.9 (C_4+C_5), 123.8 (C_3+C_6),126.25 (C_{4a}+C_{5a}), 126.3 (*orto*-Cs), 127.3 (C_7+C_2), 129.5 (*meta*-Cs), 134.9 ($C_{ipso\text{-}SO2}$), 138.3 (C_{1a}+C_{8a}), 144.8 ($C_{ipso\text{-}Me}$).

[10] Pale yellow needles (from hexane-chloroform), m.p. 145.5-150°C, **IR** (KBr): 1666, 1602, 1373, 1175. **^{1}H-NMR** ($CDCl_3$, 200 MHz): 2.31 (s, 3H, $Me_{\text{-tosyl}}$), 3.54 (br s, 2H, Hs_1), 3.9 (s, 2H, N-$C\underline{H}_2$-Ph), 5.8-5.95 (br d + dm, 2H, H_2, H_3), 6.58 (br s, 1H, H_4), 7.20 (d, 2H, *meta*-$Hs_{\text{ tosyl}}$, *J* = 8,51 Hz), 6.85-7,10 and 7.20-7.40 (br m, 13H, H_5,H_6, H_7, $Hs_{\text{-benzoyl}}$, $Hs_{\text{-benzyl}}$) , 7.64 (d, 2H, *orto*-$Hs_{\text{-tosyl}}$, *J* = 8,51 Hz) , 8.18 (d, 1H, H_8, *J* = 5.58 Hz) **^{13}C-NMR** ($CDCl_3$, 200 MHz): 20.95 (Me-tosyl), 25.95 (C_1), 48.53 (CH_2-benzyl), 53.03 (C_4), 113.78 (C_8), 125.75 (*orto*-C), 129.50 (*meta*-C), 134.54, 135.25, 135.57, 136.27, 137.28, 137.92, 144.69 ($C_{ipso\text{-}benzoyl}$, $C_{ipso\text{-}benzyl}$, $C_{ipso\text{-}tosyl}$, C_{1a}, C_{8a}, *para*-$C_{\text{-tosyl}}$), 171,6 (C=O).

[11] Despite the expenditure of much effort on the isolation of a 4-unsubstituted *N*-tosyl-dihydrocarbazole or the 4-(*N*-acyl-*N*-alkylamino)-substituted carbazole from these reactions, none was observed in any case.

[12] Attempts to obtain the D-A adduct from the reaction of 1-(N,N-diethylamino)-1,3-butadiene and N-tosyl-3-nitroindole at 50°C in a close ampoule led to the complete decomposition of the diene and 50% detosylation of the dienophile, obtaining N,N-diethyl-4-toluensulfonamide (unpublished results).

[13] In contrast, the higher temperature requirements for the cycloaddition of N-tosyl-3-acetylindole (comparatively less reactive than 3-nitroderivative) and the thermal instability of both 1-(N-acyl-N-alkylamino)-1,3-butadienes, makes this combination unsuitable for the pursued objective (unpublished results).