

Synthesis of Few Azacycl[3.2.2] Azine Derivatives

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Abstract

A novel and simple method for the synthesis of azacycl[3.2.2]azine and its derivatives is carried out with 2-phenyl-imidazo[1,2-a]pyridine and DMAD under microwave conditions in synthetically useful yields. The product 2-phenyl azacycl[3.2.2]azine was obtained in low yield. By adopting the same procedure the different 4-substituted nitro, chloro, methyl, bromo and fluoro derivatives have been synthesised.

Keywords: *Azacycl[3.2.2]azine, DMAD, Microwave, 2-phenyl-imidazo[1,2-a]pyridine*

INTRODUCTION

The heterocyclic ring compound azacycl[3.2.2]azine contains one additional N atom in the cycl[3.2.2]azine ring. Four mono azacycl[3.2.2]azines are possible¹. Azacyclazine is obtained by the substitution of a nitrogen atom instead of a carbon atom on the periphery in a nonangular position². 2-phenyl-1-azacycl[3.2.2]azine was the first synthesized compound³.

Replacement of a carbon atom in a cyclic conjugated system by N (or more C atoms by

more N) leads to disturbance of the symmetry of the π electron system⁴. This leads to nonuniform electron distribution of electric charge and the nonequivalence of bonds. With increasing nitrogen atoms, the polarity of C-N bonds increases because of decreasing electron density at the neighbouring carbon atoms and the high charge density at nitrogen atoms. This results in decrease of stabilization energy and renders the heterocyclic ring more susceptible for nucleophilic attack. W.W.Paudler⁵ et al found that 2-

azacycl[3.2.2] azine ring system is stable to aqueous acid. Azacyclazine is a heterocyclic compound with 12π electron and is an electron rich group containing nitrogen⁶.

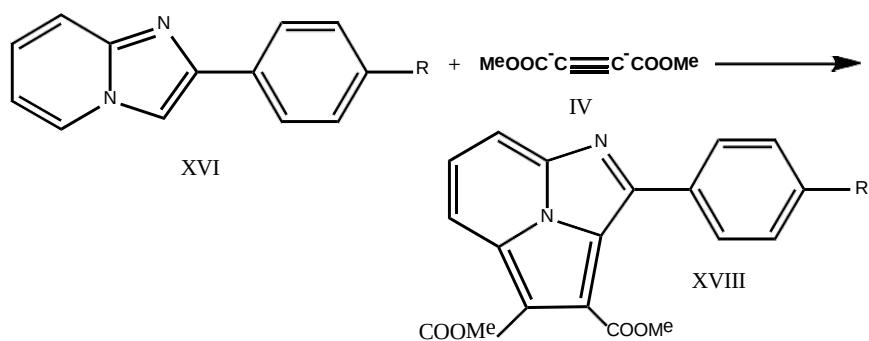
EXPERIMENTAL SECTION

Melting points were determined with a Metler melting point apparatus. All reactions were carried out in a commercially available microwave oven (Samsung M183DN) operating at 300W. IR spectra were determined on a JASCO FT/IR -4100 spectrometer using KBr. Mass spectra were measured with a Waters-3100 spectrometer. ^1H and ^{13}C NMR spectra were recorded in DMSO at room temperature on Bruker Avance III 400MHz spectrometer. Elemental analyses were conducted on the Elementarvario EL III instrument.

GENERAL PROCEDURE FOR THE SYNTHESIS OF 1-AZACYCL [3.2.2] AZINE DERIVATIVES

Imidazo[1,2-a]pyridine derivative (1mmol), DMAD (2 mmol) and K_2CO_3 (1 mg) were mixed with 1 mL of water in an Erlenmeyer flask and is fitted with a bent tube. The other end of the bent tube is connected to a receiver. The mixture was stirred and irradiated for 6 minutes at 300W with intermittent irradiation for 30 seconds (reaction monitored by TLC). After cooling to room temperature, the products were extracted with dichloromethane. The products were further purified by column chromatography using n-hexane/EtOAc, (9:1v/v). The products were recrystallized from methanol. The same procedure was adopted for the synthesis of other substituted derivatives(a-e). The synthesis of 1-azacycl[3.2.2]azine compounds(a-e) is shown in scheme 1.

RESULTS AND DISCUSSION



R= a) p- $\text{C}_6\text{H}_4\text{NO}_2$ b) p- $\text{C}_6\text{H}_4\text{Cl}$, c) p- $\text{C}_6\text{H}_4\text{Me}$, d) p- $\text{C}_6\text{H}_4\text{Br}$, e) p- $\text{C}_6\text{H}_4\text{F}$

Scheme 1 Synthesis of 1-azacycl[3.2.2]azines (a-e).

The proposed mechanism of the reaction (Fig. 1) can be depicted as follows. 4-Substituted 2-phenyl imidazo[1,2-a]pyridine (XVI) on (3+2) cycloaddition with one molecule of DMAD (IV) gave dihydro derivative (XVII) which on aerial oxidation give rise to the final product 1-azacycl[3.2.2]azine derivative (XVIII).

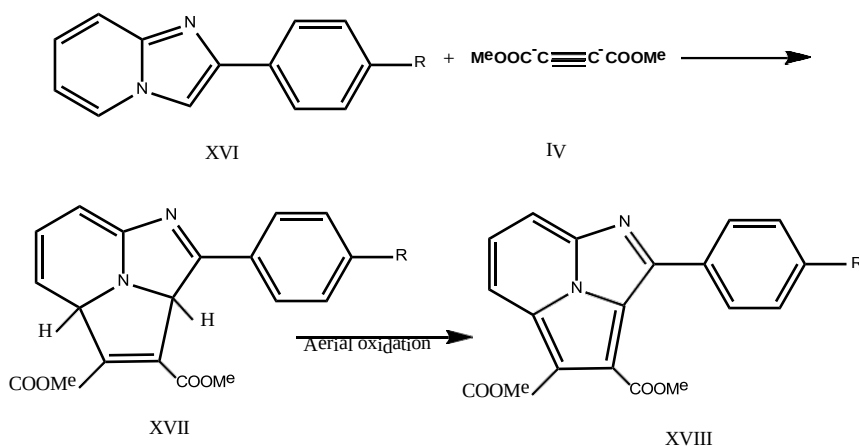


Fig 1 Mechanism of Synthesis of azacycl[3.2.2]azine

a) 2-(4-Nitrophenyl)-4,5 dicarbomethoxy-1-azacycl[3.2.2]azine

0.24 g of p-nitrophenylimidazo[1,2-a]pyridine (1mmol) was treated with 1.2 mL of DMAD and 1mg of K_2CO_3 and subjected to microwave irradiation in a domestic microwave oven for 6 minutes in presence of 1mL of water. The product was extracted with dichloromethane and finally recrystallised from methanol (yield-98mg, 33%) m.p.93-95°C. The compound was identified as 2-(4-nitrophenyl)-1-azacycl[3.2.2]azine.

Elemental Analysis for $C_{19}H_{13}N_3O_6$ (nitro derivative):

Calculated: C 56.05; H 2.15; N 9.8; Found: C 56.77; H 2.75; N 8.13.

IR (KBr cm^{-1}): 1724, 1703(C=O), 1568(-NO₂), 1312, 1142, 708.

¹H NMR(400 MHz,DMSO): δ 8.03 (2H, J=7.4Hz); δ 8.12 (2H,J=7.4Hz); δ 7.54-6.65 (m, 3H); δ 3.17 (s, 3H); δ 3.43 (s, 3H).

¹³C NMR(400MHz,DMSO): 164.3(2C), 133.4, 129.3, 126.2, 125.1, 124.4, 120.6, 120.4, 117.8, 113.5, 113.3, 112.0, 110.9, 110.2, 51.3(2C).

Mass m/z : 379 [M⁺]

b) 2-(4-Chlorophenyl)-4,5-dicarbomethoxy-1-azacycl[3.2.2]azine

0.23 g of p-chlorophenylimidazo[1,2-a]pyridine (1mmol) was treated with 1.2 mL of DMAD and 1mg of K₂CO₃ and subjected to microwave irradiation in a domestic microwave oven for 6 minutes in presence of 1mL of water. On recrystallisation from methanol the compound appeared as greenish red crystals. (yield-113mg, 61%) m.p.143-145 °C.

Elemental Analysis for C₁₉H₁₃N₂O₄Cl (Chloro derivative):

Calculated: C 58.13; H 4.21; N 8.68; Found: C 57.42; H 4.37; N 8.73.

IR (KBr cm⁻¹): 1747, 1618,1368,1297,1106, 658.

¹H NMR(400 MHz,DMSO): δ 8.12 (d, 2H, J=7.2Hz); δ 7.54 (d, 2H, J=7.2 Hz); δ 7.45-6.45 (m, 3H); δ 3.54 (s, 3H); δ 3.45 (s, 3H).

¹³C NMR(400MHz,DMSO): 162.4(2C), 133.8, 128.4, 126.7, 126.3, 125.2, 121.7, 120.8, 118.6, 112.5, 112.1, 111.9, 110.7, 108.2, 52.4(2C).

Mass m/z: 368 [M⁺]

c) 2-(4-Methylphenyl)-4,5-dicarbomethoxy-1-azacycl[3.2.2]azine

0.21 g of p-methylphenylimidazo[1,2-a]pyridine (1mmol) was treated with 1.2 mL of DMAD and 1mg of K₂CO₃ and subjected to microwave irradiation in a domestic microwave oven for 6 minutes in presence of 1mL of water. On recrystallisation from methanol the compound appeared as red crystals. (yield-157mg, 46%) m.p.110- 112 oC

Elemental Analysis for C₂₀H₁₆N₂O₄ (Methyl derivative):

Calculated: C 57.88; H 4.43; N 4.78; Found: C 57.67; H 3.53; N 4.21.

IR (KBr cm⁻¹): 1752(C-CH₃), 1718, 1246, 1286, 1123, 783.

¹H NMR(400 MHz,DMSO): δ 8.24 (d, 2H, J=7.2Hz); δ 7.85 (d, 2H, J=7.2Hz); δ 7.46-6.74 (m, 3H); δ 3.53 (s, 3H); δ 3.44 (s, 3H); δ 2.23 (s, 3H).

¹³C NMR(400MHz,DMSO): 161.7(2C), 132.5, 127.3, 126.6, 126.1, 124.7, 122.4, 121.3, 117.5, 112.4, 112.2, 111.4, 110.5, 107.7, 51.8(2C), 21.4.

Mass m/z : 348 [M⁺]

d) 2-(4-Bromophenyl)-4,5-dicarbomethoxy-1-azacycl[3.2.2]azine

0.27 g of p-bromophenylimidazo[1,2-a]pyridine (1mmol) was treated with 1.2 mL of DMAD and 1mg of K₂CO₃ and subjected to microwave irradiation in a domestic microwave oven for 6 minutes in presence of 1mL of water. On recrystallisation from methanol the compound appeared as green crystals. (yield-137mg, 69%) m.p. 87-89°C.

Elemental Analysis for C₁₉H₁₃N₂O₄Br(bromo derivative):

Calculated: C 55.42; H 4.43; N 3.21; Found: C 54.52; H 4.64; N 3.83.

IR (KBr cm⁻¹): 1732, 1664(arylC=O), 1298, 1276, 1145, 674.

¹H NMR (400 MHz,DMSO): δ 8.2 (d, 2H, J=7.4Hz); δ 7.8 (d, 2H, J=7.4 Hz); δ 7.54-6.63 (m, 3H); δ 3.44 (s, 3H); δ 3.32 (s, 3H).

¹³C NMR(400MHz,DMSO): 162.8(2C), 133.4, 126.7, 126.2, 126.1, 125.5, 123.1, 122.3, 118.4, 113.1, 112.5, 111.2, 109.5, 104.3, 53.2(2C).

Mass m/z : 413 [M⁺]

e) 2-(4-Fluorophenyl)-4,5-dicarbomethoxy-1-azacycl[3.2.2]azine

0.21 g of p-fluorophenylimidazo[1,2-a]pyridine (1mmol) was treated with 1.2 mL of DMAD and 1mg of K₂CO₃ and subjected to microwave irradiation in a domestic microwave oven for 6 minutes in presence of 1mL of water. On recrystallisation from methanol the compound appeared as greenish crystals. (yield-142mg, 53%) m.p. 130-132°C.

Elemental Anal. for C₁₉H₁₃N₂O₄F (fluoro derivative):

Calculated: C 53.22; H 4.82; N 3.73; Found: C 54.14; H 4.74; N 3.17.

IR (KBr cm⁻¹): 1748, 1704(C=O), 1264, 1213, 1131, 779.

¹H NMR(400 MHz,DMSO): δ 8.16 (d, 2H, J=7.2Hz); δ 7.56 (d, 2H, J=7.2Hz); δ 7.34-6.65 (m, 3H); δ 3.47 (s, 3H); δ 3.35 (s, 3H).

¹³C NMR(400MHz,DMSO): 162.4(2C), 131.5, 130.7, 129.2, 122.1, 120.5, 120.1, 117.3, 116.4, 116.1, 111.5, 107.2, 52.6(2C).

Mass m/z: 352 [M⁺]

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CONCLUSION

A simple method was developed for the synthesis of 1-azacycl[3.2.2]azines. The microwave technology adopted here is a highly acceptable. The reaction was carried out in aqueous medium which is pollution free and cost effective. Five derivatives of 1-azacycl[3.2.2]azines were synthesised by this simple technique.

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