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Utility of Vilsmeier- Haack reaction in the cyclization of heterocycles: synthesis of phenyl-dibenzo[b,h][1,6] naphthyridines

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ABSTRACT

Three novel phenyl-dibenzo [*b, h*][1,6]naphthyridine derivatives were synthesized in five steps, from ethyl benzoyl acetate and aniline derivatives. A total of 48 minutes reaction time was recorded for the latter four steps using microwave irradiation. The yield of the final products and all intermediate products were over 80%.

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Introduction

Heterocyclic compounds are widely distributed in nature and are essential to life as they play a vital role in the metabolism of all living cells. There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use; these include natural products as well as synthetic analogues. Antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine and reserpine, and cardiac glycosides such as those of digitalis are some typical examples.[1-5]

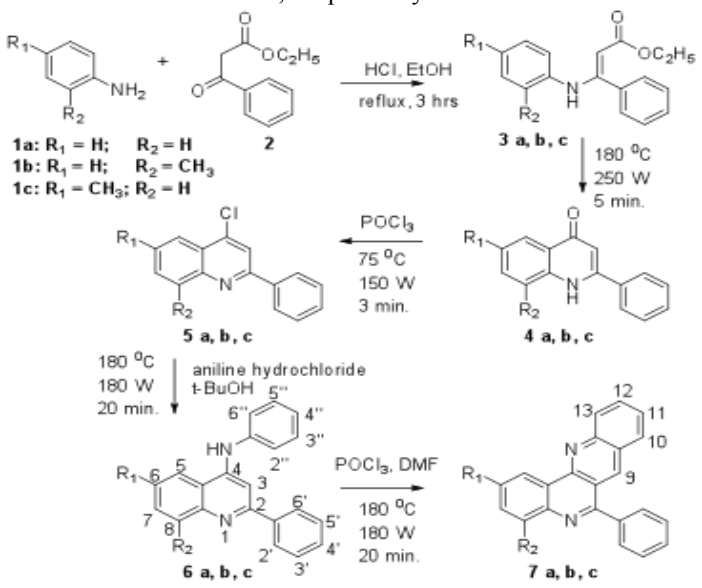
Among the nitrogen heterocycles, naphthyridines and their derivatives represent an important class of organic molecules since they are applied as pharmaceuticals, fungicides, bactericides, herbicides and insecticides as well as are useful synthetic blocks in the preparation of several alkaloids.[6-9] In view of these properties; the synthesis of naphthyridine type drugs is attractive for biological studies.

Although many synthetic methods, using several reaction steps[10-13] as well as one pot two-component[14, 15] and multi-component[16] systems are reported for naphthyridines, there still exists a demand for active research investigations of alternate synthetic approaches to new products possessing potential biological applications.

Results and discussion

For the past two decades our research group is concentrating on the synthesis of fused naphthyridines[17,18] however the most articulated work on these studies was the synthesis of 7-methyldibenzo[*c,f*][2,7]naphthyridin-6(5*H*)-ones *via* three routes.[18] Our recent publication explored the synthesis of compounds **3a-c**, **4a-c**, **5a-b** and **6a-c** by using conventional and microwave methods.[19,20] The thrust of our research is 'conservation and less consumption of energy', to generate available drugs with higher consumer value. Hence we followed up our recent procedure[21] to construct **3a-c** to **6a-c** and decided to study the Vilsmeir-Haack reaction to improve on the synthesis of important organic molecules.

Herein we synthesized 6-Phenyl-dibenzo[*b,h*][1,6]naphthyridine **7a**, 4-methyl-6-phenyl-dibenzo[*b,h*][1,6] naphthyridine **7b** and 2-methyl-6-phenyl-dibenzo[*b,h*][1,6]naphthyridine **7c** from their respective anilinoquinoline **6a**, **6b** and **6c**. The yield of **7a**, **7b** and **7c** were 90, 87 and 77 %, respectively. The ^{1}H NMR spectrum of **7a** shows aromatic signals at δ 8.20 (H-9); 8.1 (H-10); 7.60 (H-11); 7.77 (H-12) and 7.79 (H-13). Also the H-3 signal of **6a** at δ 6.94 is absent due to ring closure. The ^{13}C NMR spectrum indicates an increased number of resonances in the aromatic region and an upfield shift of C-3 signal to δ 119.1. The ^{1}H NMR spectrum of **7b** and **7c** are similar to **7a** except that a three proton singlet at δ 1.55 and 2.57 is evident for the methyl group of their respective Ar-CH_3. The ^{13}C NMR spectra of **7b** and **7c** shows the methyl carbon at δ 16.8 and 21.86, respectively.



Scheme 1

Tele:

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Experimental

Materials, methods and instruments

All chemicals were purchased from Sigma, South Africa. The reaction progresses were monitored by TLC using pre-coated silica gel (thickness 0.25mm) aluminium backed plates with a fluorescent indicator. Individual compounds were isolated by column chromatography on silica gel 60 (Merck particle size 0.040 - 0.063 mm). Microwave-assisted reactions were conducted using a microwave synthesizer (CEM Discover). Proton and carbon NMR spectra, recorded at 400 MHz, were obtained from a Bruker ultra shield spectrometer. Chemical shifts are reported in parts per million (ppm) relative to the peak of tetramethylsilane as internal standard; *J* values are given in Hz. Infra-red (IR) spectra were recorded on a Perkin Elmer 100 FT-IR spectrometer. Mass spectrometric data was obtained using a Bruker micro TOF- Q11. Melting points were determined from a Stuart SMP 3 melting point apparatus using open-ended capillary tubes. All melting points are uncorrected.

General procedure for the synthesis of 6-phenyl-dibenzo[*b,h*] [1,6]Naphthyridines 7a, 7b and 7c.

$POCl_3$ (12.95 ml) was added, drop-wise with stirring, to cold DMF (3.85 ml). The mixture was stirred for 30 minutes, cooled to 5º C and **6a** or **6b** or **6c** (0.012 mol) was added. This mixture was stirred for 30 minutes and heated under microwave conditions at 75ºC and 120 watts for 20 minutes. The mixture was cooled to room temperature and carefully poured into 500 ml ice cold water. With stirring, 5 ml of a 25% sodium carbonate solution was added to neutralise the solution. The precipitate was filtered, air dried and subjected to column chromatography using hexane: ethyl acetate (4:1) as eluent.

7a. Yield 90 %, mp 159 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz, $CDCl_3$ = 7.24 ppm) δ 8.18 d (1H, J=8.5, H-5), 7.60-7.79 m (6H, H-6, H-7, H-8, H-11, H-12, H-13), 7.47-7.54 m (3H, H-3′, H-4′, H-5′), 8.11-8.23 m (4H, H-9, H-10, H-2′, H-6′). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm): 157.29 (C-2), 119.1 (C-3), 138.6 (C-4 , C-9), 123.9 (C-4a, C-13), 125.3 (C-5), 127.2 (C-6 , C-11), 130.1 (C-7,C-10, C-12,), 128.9 (C-8, C-13), 149.1 (C-8a), 130.6 (C-9a), 143.2 (C-13a), 137.1 (C-1′), 127.5 (C-2′, C-6′), 129.8 (C-3′C-5′), 127.2 (C-4′).

7b. Yield 87 %, mp 183 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz, $CDCl_3$ = 7.24 ppm) δ 1.55 s (3H, Ar-CH_3), 8.06 d (2H, J=8.4, H-5, H-10), 7.61-7.79 m (4H, H-6, H-7, H-11, H-12), 7.99-8.23 m (4H, H-9, H-13, H-2′, H-6′), 7.47-7.54 m (3H, H-3′, H-4′,H-5′).^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm): 16.8 (Ar-CH_3), 155.3 (C-2), 118.4 (C-3), 138.2 (C-4), 121.8 (C-4a), 125.25 (C-5), 126.9 (C-6), 130.6 (C-7, C-12 , C-9a), 138.8 (C-8), 148.0 (C-8a), 138.2 (C-9, C-1′), 129.7 (C-10), 127.4 (C-11), 121.8 (C-13), 143.3 (C-13a), 127.4 (C-2′, C-6′), 128.9 (C-3′, C-5′), 126.8 (C-4′).

7c. Yield 77 %, mp 89 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz, $CDCl_3$ = 7.24 ppm) δ 2.57 s (3H, Ar-CH_3), 7.60 s (1H, H-5), 7.47-7.59 m (5H, H-7, H-11, H-3′, H-4′, H-5′); 7.92-8.12 m (6H, H-8, H-10, H-13, H-10, H-2′, H-6′). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.6 (Ar-CH_3), 156.4 (C-2), 119.1 (C-3), 137.4 (C-4), 122.8 (C-4a), 125.2 (C-5), 137.5 (C-6), 132.0 (C-7, C-12), 128.9 (C-8), 147.7 (C-8a), 138.9 (C-9), 132,8 (C-9a), 132.4 (C-10), 127.0 (C-11), 129.8 (C-12), 122.7 (C-13), 142.4 (C-13a), 137.0 (C-1′), 128.9 (C-2, C-6′), 129.8 (C-3, C-5′), 127.4 (C-4′).

Conclusion

The use of microwave irradiation provided an efficient, rapid and practical method for the synthesis of phenyl substituted-dibenzo [*b,h*] [*1,6*] naphthyridines. This is a highly efficient microwave reaction requiring only a total reaction time of 48 minutes in 4 simple steps. High yields were obtained for all intermediates as well as the final product.

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