# A NOVEL SYNTHESIS OF BENZO[g]IMIDAZO[1,2-a]PYRIDINES: THE REACTIVITY OF ARYLIDINE-1H-BENZIMIDAZOLE-2-ACETONITRILE WITH ELECTRON POOR OLEFINS AND DIMETHYLACETYLENE DICARBOXYLATE UNDER MICROWAVE IRRADIATION

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## Abstract:

Arylidine-1H-benzimidazole-2-acetonitriles reacted with β-nitrostyrene, acrylo-nitrile and dimethylacetylene dicarboxylate under microwave irradiation to afford benzo[g]-imidazo[1,2-a]pyridines in high yields.

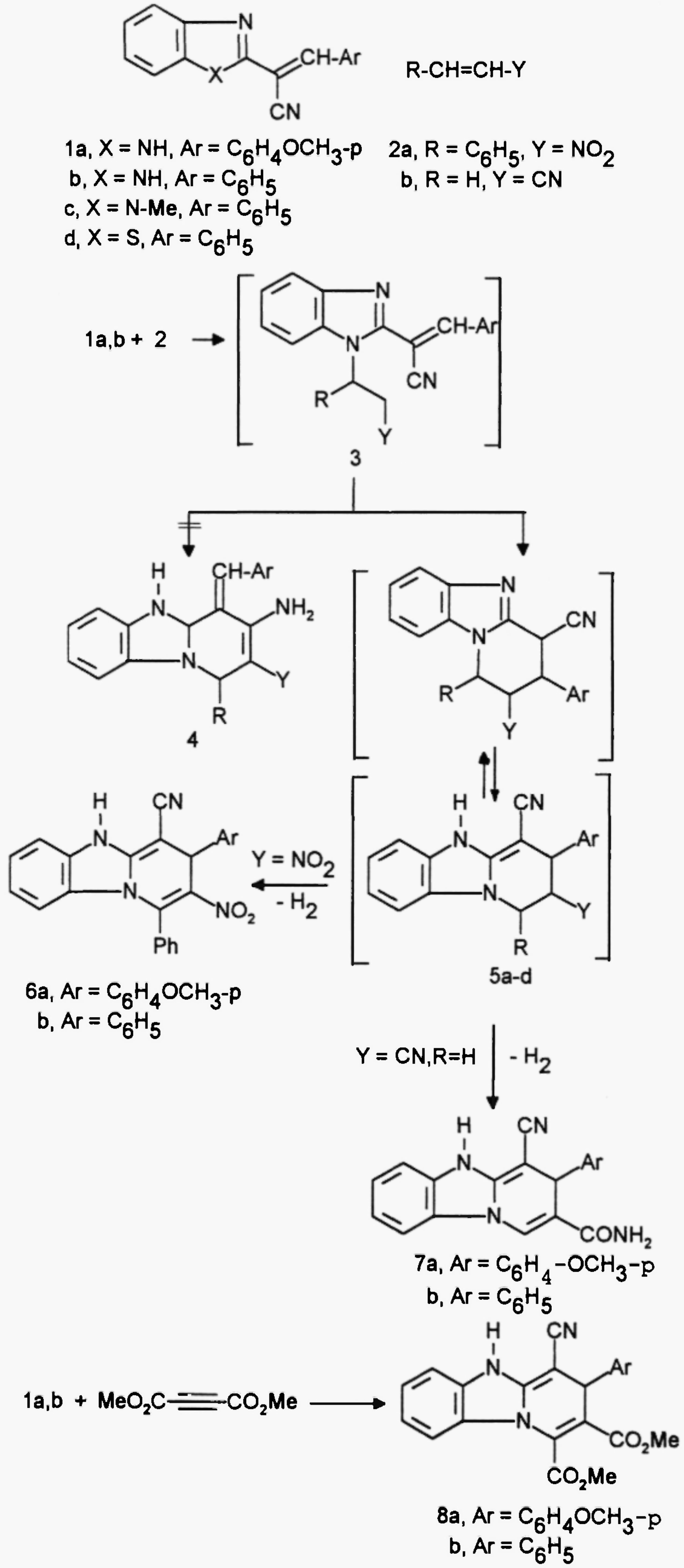
## Introduction

Benzimidazo[1,2-a]pyridines have received increasing interest over the past years (1) owing to their biological activities. For example, many of their derivatives are known as antifungal, anthelimintic and local anesthetic agents (2). The organic synthesis under microwave heating technique and without solvent is now receiving considrable interest (3,4). It is worth to mention that this technique offers several advantages : solvents are usually toxic, expensive, difficult to remove in the case of aprotic dipolar solvents with high boiling points and are environments air polluting agents.

## Results and Discussion

As a part of our program aiming to synthesis polyfunctionally substituted condensed heterocycles via simple routes and unexpensive starting materials (5,6) , we report here a novel synthesis of benzo[g]imidazo[1,2-a]pyridines by reaction of arylidine-1H-benzimidazole-2-acetonitriles **1a,b** with β-nitrostyrene, acrylonitrile and dimethylacetylene dicrboxylate under microwave irradiation. After heating compound **1a** with β-nitrostyrene **2a** in several solvents during 48 hours, most of **1a** was recovered unchanged. In contrast, when experiment was conducted without solvent in a conical flask under microwave irradiation (500 w, 12 minutes) a compound of molecular formula $C_{25}H_{18}N_4O_3$ ($M^+ = 422$ m/e) was obtained. Two isomeric structures seemed possible for the reaction product (cf. Structure **4** and **6a**). Structure **4** was ruled out based on IR spectra which revealed the presence of a CN function at 2200 $cm^{-1}$. Structure **6a** was established for the reaction product based on its $^1H$ NMR spectrum which revealed the absence of ylidine CH proton (ca. 6.8 ppm) and the presnce of an absorption band at 4.6 ppm which was assigned for pyridine CH-4 together with a bands at 3.87 ppm for $OCH_3$ group, 8.22 ppm for NH proton and a multiplet integrated for 13H at 7.3-7.9 ppm for aromatic protons. It is difficult to rationalise for these absorptions if the reaction product was **4**. It is assumed that the formation of 6a was proceed via addition of NH of **1a** to the activated double bond in **2a** followed by intramolecular cyclization and air oxidation as demonstrated in Scheme 1. The formation of **6a** via a concerted [4+2] cycloaddition is a possibility, but it was ruled out based on the unreactivity of **1c** towards the same reagent under the same reaction condition. Also, attempts at reacting **1d** with **2a** yields unchanged product. A phenomena in support of the stepwise reaction mechanism. Similarly, **1b** reacted with **2a** to afford **6b**. Again the structure assigned for **6b** was established based on analytical and spectral data (see Experiment).

The reaction of **1a** with **2b** affords a compound of molecular formula $C_{20}H_{18}N_4O_2$ ($M^+$ = 344 m/e). Structure **7a** was established for the reaction product based on spectral data. Thus IR spectrum of **7a** showed absorption bands at 3400-3200 $cm^{-1}$ (amide $NH_2$ and NH), 2200 $cm^{-1}$ (CN) and 1670 $cm^{-1}$ (amide CO group). $^1H$ NMR showed absorptions at 7.95 ppm for NH proton, 7.2-7.5 ppm for aromatic protons and 7.0 ppm for $NH_2$ group as well as absorption at 4.7 ppm for pyridine CH-4 and 3.88 ppm $OCH_3$ group. It is assumed that the formation of **7a** was proceed via hydrolysis of the cyano function in **5c** by air moisture during irradiation. Similarly, **1b** reacts with **2b** to afford **7b** (see Scheme 1).


CH-Ar
CN
R-CH=CH-Y
1a, X = NH, Ar = C6H4OCH3-p
b, X = NH, Ar = C6H5
c, X = N-Me, Ar = C6H5
d, X = S, Ar = C6H5
2a, R = C6H5, Y = NO2
b, R = H, Y = CN
1a,b + 2
3
4
5a-d
Y = NO2
- H2
6a, Ar = C6H4OCH3-p
b, Ar = C6H5
Y = CN,R=H
- H2
7a, Ar = C6H4-OCH3-p
b, Ar = C6H5
1a,b + MeO2C—≡—CO2Me
8a, Ar = C6H4OCH3-p
b, Ar = C6H5

Scheme 1

The reaction of **1a,b** with dimethylacetylene dicarboxylate under the same reaction conditions led to the formation of **8a,b**. The structure assigned for the reaction product was established based on analytical and spectral data (see Experimental).

## Experimental

Melting points are uncorrected. -IR spectra were recorded (KBr disks) on a Shimadzu 470 spectrophotometer. -$^1$H NMR were measured on a Bruker WM 300 instrument with TMS as internal reference and chemical shifts are expressed in δ ppm. Mass spectra were obtained on a MAT instrument by EI at 70 ev. Microanalytical data (C,H,N) were obtained from the Microanalytical Data Unit at Cairo University.

**Preparation of benzo[g]imidazo[1,2-a]pyridines 6a,b; 7a,b and 8a,b : General procedure:** A mixture of **1a,b** and **2a,b** or dimethylacetylene dicarboxylate (0.01 mol) in a pyrex conical flask was irradiated at 500-600 w in Samsung MX 145 microwave oven during 10-12 minutes. After addition of ethanol (10 ml), the resulting solid product was collected by filtration and crystallized from the proper solvent.

**6a** : Yield 90 % ; m.p. 158-160 °C from ethanol, $\upsilon_{max/cm-1}$ (KBr) 3200 (NH), 2200 (CN). $\delta_H$ (DMSO) 8.22(1H,s), 7.3-7.9(13H,m),4.6(1H,s), 3.87 (3H,s). (Found: C, 71.2; H, 4.4; N, 13.3. $C_{25}H_{18}N_4O_3$ requires C, 71.08; H, 4.29; N, 13.26 % ($M^+$ = 422 m/e).

**6b** : Yield 88 % ; m.p. 142-144 °C from ethanol, $\upsilon_{max/cm-1}$ (KBr) 3100 (NH), 2200 (CN). (Found: C, 73.4; H, 4.3; N,14.4. $C_{24}H_{16}N_4O_2$ requires C, 73.45; H, 4.10; N, 14.27 % ).

**7a** : Yield 82 % ; m.p. 218-220 °C from ethanol, $\upsilon_{max/cm-1}$ (KBr) 3400-3200 (NH,$NH_2$), 2200 (CN), 1670 (amide CO). $\delta_H$ (DMSO) 7.95(1H,s), 7.2-7.5(9H,m), 7.0(2H,br), 4.7 (1H,s), 3.88 (3H,s). (Found: C, 69.9; H, 4.6; N, 16.1. $C_{20}H_{16}N_4O_2$ requires C, 69.75; H, 4.68; N, 16.26 % ($M^+$ = 344 m/e).

**7b** : Yield 80 % ; m.p. 210-212 °C from ethanol, $\upsilon_{max/cm-1}$ (KBr) 3400-3250 (NH,$NH_2$), 2200 (CN). 1670 (amide CO). (Found: C, 72.8; H, 4.6; N,17.7. $C_{19}H_{14}N_4O$ requires C, 72.59; H, 4.48; N, 17.82 % ).

**8a** : Yield 88 % ; m.p. 228-230 °C from dioxane, $\upsilon_{max/cm-1}$ (KBr) 3300 (NH), 2200 (CN) and 1710 (ester CO). $\delta_H$ (DMSO) 8.3(1H,s), 7.2-7.9(8H,m), 4.6 (1H,s),3.72(3H,s) 3.32(3H,s), 3.13(3H,s). (Found: C, 66.3; H, 4.7; N, 10.3. $C_{23}H_{19}N_3O_5$ requires C, 66.15; H, 4.58; N, 10.10% ).

**8b** : Yield 85 % ; m.p. 235-237 °C from dioxane, $\upsilon_{max/cm^{-1}}$ (KBr) 3300 (NH), 2200 (CN) and 1710 (ester CO). $\delta_H$ (DMSO) 8.2(1H,s), 7.3-7.9(9H,m), 4.8(1H,s), 3.36 (3H,s),3.22 (s,3H). (Found: C, 68.3; H, 4.5; N, 10.9. $C_{22}H_{17}N_3O_4$ requires C, 68.17; H, 4.42; N, 10.85 % ).

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## References

1. For reviews, see : H.L. Blewitt in " The Chemistry of Heterocyclic Compounds"; A. Weissberger, E.C. Taylor, Eds.; Interscience Publishers : New York, Vol. 30, p. 117 (1977). J.A. Montgomery, J.A. Secrist in " Comprehensive Heterocyclic Chemistry "; A.R. Katritzky, C.W. Ress, Eds.; Pergamon Press; Oxford, Vol. 5, p. 607 (1984).
2. M.H. Fisher, A.Lusi, J. Med. Chem., 15, 982 (1972); G. Grassy, J.C. Teulade, J.P. Chapat, M.S. de Buochberg, M. Atisso, Eur. J. Med. Chem., 17, 109 (1982). P.J. Sanfilippo, M. Urbanski, J.B. Press, B. Dubinsky, J.B. Moore, J.Med. Chem., 31, 2221 (1988).
3. M. Rahmouni, A. Derdour, J. Bazureau, J. Hamelin, Tetrahedron Lett., 4563 (1994).
4. S.A.El Ayoubi, F.T. Boullet, J. Hamelin, Synthesis, 258 (1994),.
5. R.Mekheimer, N.K. Mohamed, E.T. Khader, K.U. Sadek, H.H. Otto, J. Chem. Res.(S), 226, (1994).
6. K.U. Sadek, M.H. Elnagdi, Synthesis, 483 (1988).

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