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Microwave Assisted Synthesis of Fused Benzimidazoles

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Microwave assisted synthesis of some benzimidazo[1,2-c]-quinazolines and benzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazolines from the reaction of suitable functionalized benzimidazole and benzimidazoquinazolines with triethylorthoesters in solvent-free conditions is described. In comparison with classical conditions the reactions are faster and the yields are higher under microwave irradiation.

Key Words: Benzimidazo[1,2-c]quinazolines, Benzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazolines, Microwave irradiation, Triethylorthoesters.

INTRODUCTION

The interest in the synthesis of fused benzimidazoles[1,2] emerges from the numerous reports on their diverse biological activities such as antiinflammatory[3,4], antiamoebic and analgesic[5,6], anticancer[7,8], antivira[9], antimicrobial[10] and anticonvulsants[11] activity. A literature survey reveals that microwave promoted solvent-free cyclization of 2-(1*H*-benzimidazol-2-yl)aniline and 6-hydrazinobenzimidazo[1,2-c]quinazolines with triethylorthoesters has not been reported.

In recent years, microwave assisted reactions have attracted much research interest because of the simplicity in operation and enhanced reaction rates. Thus, microwave irradiation which has become a powerful synthetic tool for the rapid synthesis of a variety of biologically active compounds is used to enhance the rates of classical organic reactions[12-14].

Prompted by these findings and interest in utilization of microwave irradiation for the synthesis of heterocyclic compounds[1,15-17], in this paper a rapid and efficient synthesis of some benzimidazo[1,2-c]quinazolines (**2a-c**) and benzimidazo[1,2-c]-[1,2,4]triazolo[4,3-a]quinazolines (**4a-f**) through cyclocondensation of 2-(1*H*-benzimidazol-2-yl)aniline (**1**) and 6-hydrazinobenzimidazo[1,2-c]quinazolines (**3a-b**) with triethylorthoesters under microwave irradiation in solvent-free conditions is reported (**Scheme-I**).

EXPERIMENTAL

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

General procedure for the preparation of benzimidazo[1,2-c]quinazolines (2a-c) and benzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazolines (4a-f):

Method A: A mixture of 2-(1*H*-benzimidazol-2-yl) aniline[18] (**1**) (1 mmol) or 6-hydrazinobenzimidazo[1,2-c]quinazolines[2] (**3a-b**) (1 mmol) and triethylorthoesters (1.5 mmol) was subjected to microwave irradiation at 800 w for the indicated time. After the completion of the reaction, which was monitored by TLC, the crude product was collected and recrystallized from *n*-hexane/chloroform and or ethanol to give compounds **2a-c** and **4a-f** in 79-90 % yields (Table-1).

TABLE-1
COMPARISON OF TIME AND YIELDS ON THE FORMATION OF COMPOUNDS **2a-c** AND **4a-f** USING MICROWAVE IRRADIATION AND CONVENTIONAL HEATING

Entry	Microwave irradiation (Method A)		Conventional heating (Method B)		m.p. (ºC)	t_c/t_{mw}
	Time (min) t_{mw}	Yield (%)[a]	Time (min) t_c	Yield (%)[a]		
2a	5	88	70	71	230-231	14.0
2b	6	82	80	69	177-179	13.3
2c	6	86	80	73	128-130	13.3
4a	5	79	60	70	360-362[2]	12.0
4b	5	90	60	75	346-348[2]	12.0
4c	7	82	70	70	319-321[2]	10.0
4d	6	89	60	81	352-354[2]	10.0
4e	7	87	70	78	339-341[2]	10.0
4f	9	84	75	73	308-310[2]	8.3

[a]Isolated yields.

Method B: The same mixtures as in above were heated under reflux in ethanol (20 mL) for the indicated time. After the completion of the reaction, which was monitored by TLC, the solvent was evaporated *in vacuo*. The crude product was collected and recrystallized from *n*-hexane/chloroform and or ethanol to give compounds **2a-c** and **4a-f** in 69-81 % yields (Table-1).

Spectral data for new compounds 2a-c

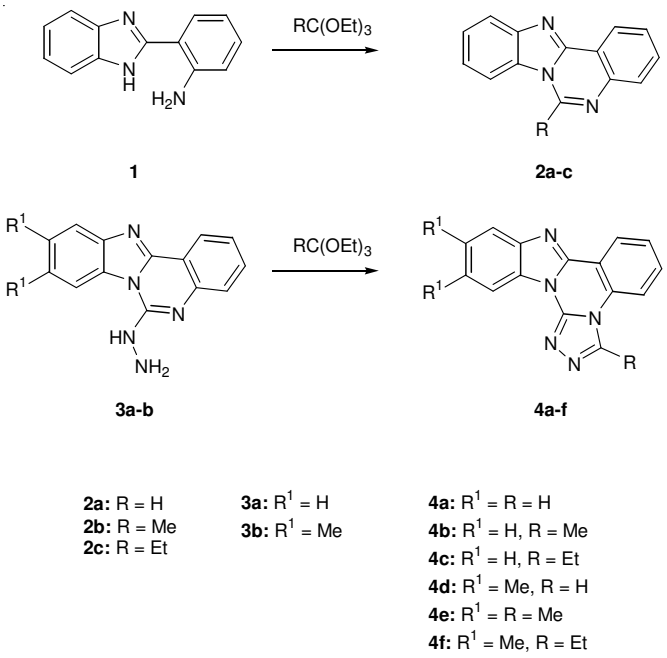
Benzimidazo[1,2-c]quinazoline (2a): ^{1}H NMR ($CDCl_3$, δppm): 7.40-8.80 (m, 8H, arom-H), 9.15 (s, 1H, CH-pyrimidine ring); MS, m/z: 219 (M^+).

6-Methylbenzimidazo[1,2-c]quinazoline (2b): ^{1}H NMR (DMSO-d_6, δppm): 3.14 (s, 3H, CH_3), 7.30-8.65 (m, 8H, arom-H); MS, m/z: 233 (M^+).

6-Ethylbenzimidazo[1,2-c]quinazoline (2c): ^{1}H NMR ($CDCl_3$, δppm): 1.55 (t, 3H, CH_3), 3.45 (q, 2H, CH_2), 7.30-8.75 (m, 8H, arom-H); MS, m/z: 247 (M^+).

RESULTS AND DISCUSSION

First, treatment of **1** or **3a-b** with triethylorthoesters using microwave irradiation in solvent-free conditions were explored (**Scheme-I**). Thus, the reactants were ground together and then irradiated at 800 w for the indicated time to give the products **2a-c** and **4a-f**, respectively (Table-1). The structure of new products **2a-c** were established from their spectral data and for known compounds **4a-f** by comparison with authentic samples.



1 **2a-c**

3a-b **4a-f**

2a: R = H
2b: R = Me
2c: R = Et

3a: R^1 = H
3b: R^1 = Me

4a: R^1 = R = H
4b: R^1 = H, R = Me
4c: R^1 = H, R = Et
4d: R^1 = Me, R = H
4e: R^1 = R = Me
4f: R^1 = Me, R = Et

Scheme-I. Preparation of compounds **2a-c** and **4a-f**

In order to draw a comparison between microwave irradiation and conventional heating for preparation of the compounds **2a-c** and **4a-f**, a mixture of **1** or **3a-b** and triethylorthoesters in ethanol was heated under reflux for the indicated time (Table-1). By comparing the data in Table-1, it is obvious that the microwave irradiation approach is faster and the yields are higher than conventional heating method.

Conclusion

In conclusion, a facile and efficient approach for the synthesis of benzimidazo-[1,2-c]quinazolines **(2a-c)** and benzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazolines **(4a-f)** under microwave irradiation in solvent-free conditions and also by thermal heating is developed. In comparison, the reactions carried out with the assistance of microwave technique are faster and the yields are higher than conventional method.

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