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A Facile Synthesis of 6-Substituted Benzimidazo[1,2-c]-Quinazolines Under Microwave Irradiation

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A FACILE SYNTHESIS OF 6-SUBSTITUTED BENZIMIDAZO[1,2-*c*]-QUINAZOLINES UNDER MICROWAVE IRRADIATION

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Abstract: Microwave irradiation promoted the high-yield cyclocondensation of ortho esters (**1a-f**) with 2-(2-aminophenyl)benzimidazole (**2**), as the catalyst was no longer needed.

There are many reports on the catalyzed reaction of ortho esters with 2-substituted amino aromatics,[1] even under microwave irradiation,[2] providing heterocycles. We wish to introduce microwave irradiation herein as the sole condition used to promote the hitherto unreported reaction between ortho esters and 2-(2-aminophenyl)benzimidazole (**2**). The reaction is simple and conducts to almost pure 6-substituted benzimidazo[1,2-*c*]quinazolines (**4a-f**) (see Scheme 1). Benzimidazoquinazolines have important properties[3] and recently were proposed as new class of antitumor compounds.[4]

No products could be obtained in the absence of solvent. Thus, in the present work we used *N*,*N*-dimethylacetamide in terms of its high substrate

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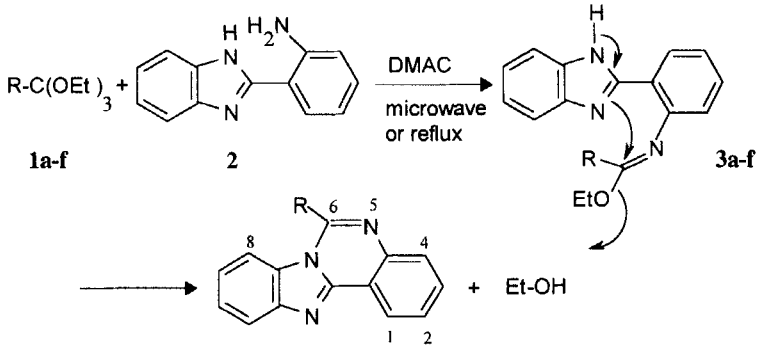
Scheme 1: Reaction of ortho esters with 2-(2-aminophenyl)benzimidazole



1a-f **2** **3a-f**

4 a-f

a; R = H, b; R = Me, c; R = Et, d; R = Pr, e; R = Bu, f; R = Ph

Table 1: Results of the reactions

product	R	microwave [a] time (min.)	microwave yield %	reflux [b] time (h)	reflux yield %
4a	H	2	85	1.5	87
4b	Me	6	89	3.5	84
4c	Et	6	94	4	93
4d	n-Pr	6	91	4	88
4e	n-Bu	6	93.5	4	91
4f	Ph	6	92	4	90

[a] Total irradiation time, irradiation was carried out in two stages with a cooling time between them. [b] Gently at 140 °C.

solubility and microwave energy transfer. The results obtained from microwave and refluxing modes of performing the reaction are shown in Table 1.

The importance of the solvents is better shown in Table 2 which indicates the result of the reaction of (**1f**) with (**2**) in some media. The reaction was accelerated in polar and high-boiling solvents, because such solvents can rapidly

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Table 2: The effect of solvent on the reaction of (**1f**) with (**2**) under microwave

solvent	toluene	THF	DMF	nitrobenzene	1,2,4-trichlorobenzene
power (watt)	385	385	210	210	385
time (min.)	15	15	6	6	15
yield (%)	none	none	90	92	69

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absorb and accumulate microwave energy. The mechanism of this reaction presumably involves the intermediacy of imidic esters [5] (**3a-f**), which subsequently cyclize to afford the products (**4a-f**).

The assignments of the structure of products were based on ^{1}H and ^{13}C-nmr, ir and mass spectral data along with CHN-microanalysis. The mass spectra of compounds (**4a-c,f**) displayed molecular ions as the base peaks, but for (**4d,e**) the base peak is a fragment tallying to (**4b**) molecular ion. The intensity of this fragment can be evidenced to the pronounced McLafferty-type fragmentation at substituent chains. Ionization of two nitrogens other than N_5 may be events raised to α-cleavage and elimination of alkenes from (**4c-e**) by a similar mechanism. As is evident from spectra, loss of HCN is the prevalent fragmentation and the peak m/e 192 is common to them. Structure of this fragment corresponds to the [2-phenylbenzimidazole] - 2H molecular ion, as the spectrum below m/e 192 is very similar to that of 2-phenylbenzimidazole.[6]

The characteristic down-field shift of C_1-H from other protons of the parent skeleton is also apparent in the ^{1}H-nmr of all products. This shift in (**4f**) is

accompanied by an up-field shift of C_8-H, which senses the shielding region of the phenyl substituent. The ^{13}C-nmr of products showed the signals for all carbon atoms.

In summary, we have succeeded in developing a convenient and rapid method for preparing (**4a-f**) in yields higher than those previously reported.[8,9] This investigation also emphasizes on microwave irradiation as the main factor in promoting the condensation of ortho esters with the amino group.

Experimental

Melting points were measured on a Mettler FP5 and are uncorrected. Elemental analyses for C,H and N were performed using a Heracus CHN-O-Rapid analyzer. IR spectra were obtained in KBr wafers on Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C nmr spectra were measured in $CDCl_3$-TMS, with a JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively. Mass spectra were recorded on a Shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV. Microwave irradiation were carried out in a National oven, Model 5250 at 2450 MHz. Chemicals were obtained from Fluka and were used without further purification.

General procedure under microwave irradiation: A mixture of 2-(2-aminophenyl)benzimidazole (**2**) [7] (2 mmole), ortho ester (**1a-f**) (1 ml in each case) and DMAC (1 ml) was placed in a tall beaker. The beaker was covered with a stemless funnel and then irradiated in the microwave oven for $t_1 = 3$ min with a power of 210 W. After a cooling time of about 5 min in room temperature the

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beaker was irradiated again for $t_2 = 3$ min at 210 W. The resultant residues were recrystalized in proper solvents which are mentioned below. In the case of (**4a**) the optimum yield was achieved through $t_1 = t_2 = 1$ min.

General procedure under classical heating: A stirred mixture of 2-(2-aminophenyl)benzimidazole (**2**) (2 mmole), ortho ester (**1a-f**) (1 ml) and DMAC (1 ml) was refluxed gently for 1.5- 4h (Table 1) under nitrogen. After this time the reaction mixture was cooled to room temperature and the white precipitate thus obtained was filtered off and then recrystalized.

Benzimidazo[1,2-*c*]quinazoline (4a): Colorless needles (from $CHCl_3$ / heptane); mp = 229.5-230 °C, lit.[8] mp = 229 °C. IR (cm^{-1}); 1622, 1602, 1514, 1467, 1450, 763, 739. ^{1}H-nmr δ(ppm); 9.05 (s, 1 H, C_6-H), 8.65 (dd, 1 H, J 6.5 Hz and 1.3 Hz, C_1-H), 8.1-7.1 (m, 7 H). ^{13}C-nmr δ(ppm); 147.61, 145.29, 143.86, 129.41, 120.57 (5 C), 137.43 (C_6), 133.07, 129.94, 129.81, 127.45, 125.50, 124.56, 121.59, 111.37 (8 CH). MS m/z (%); 219 (M^+, 100), 192 (M^+-HCN, 4.7), 164 (5.7), 129 (9.4), 110 (M^{++}, 9.5), 102 (10.4), 91 (9.4), 77 (7.5), 64 (13.2), 51 (10), 39 (13.7).

6-Methyl benzimidazo[1,2-*c*]quinazoline (4b): Colorless crystals (from ethanol); mp = 179 °C, lit.[8] mp = 176-177 °C. IR (cm^{-1}); 1621, 1598, 1527, 1441, 1420, 773, 760, 749. ^{1}H-nmr δ(ppm); 8.4 (dd, 1H, J 6 Hz and 1.5 Hz, C_1-H), 7.9-7.05 (m, 7 H), 2.9 (s, 3 H, C_6-CH_3). ^{13}C-nmr δ(ppm); 147.21 (2 C), 143.91, 141.87, 128.88, 117.68 (4 C), 131.28, 127.25, 127.01, 125.10, 123.71, 122.53, 119.72, 113.57 (8 CH), 23.74 (CH_3). MS m/z (%); 233 (M^+, 100), 207 (MH^+-

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HCN, 10.4), 192 (5.7), 164 (6.6), 117 (M^{++}, 11), 102 (13), 90 (8), 77 (6.5), 63 (12.3), 51 (8.5), 39 (11.3).

6-Ethyl benzimidazo[1,2-*c*]quinazoline (4c): Colorless needles (from benzene/ heptane); mp = 126 °C. Calculated for $C_{16}H_{13}N_3$; C 77.71, H 5.30, N 16.99 %. Found; C 77.7, H 5.2, N 16.8 %. IR (cm^{-1}); 1622, 1601, 1528, 1439, 1418, 778, 758, 739. ^{1}H-nmr δ(ppm); 8.62 (dd, 1 H, J 6 Hz and 1.8 Hz, C_1-H), 8.1-7.2 (m, 7 H), 3.35 (q, 2 H, J 7.2 Hz, CH_2), 1.52 (t, 3 H, J 7.2 Hz, CH_3). ^{13}C-nmr δ(ppm); 150.87, 147.25, 143.91, 141.79, 128.43, 117.68 (6 C), 131.08, 127.23, 127.00, 124.85, 123.63, 122.41, 119.64, 113.94 (8 CH), 28.83 (CH_2), 9.81 (CH_3). MS m/z (%); 247 (M^+, 69), 246 (M^+-H, 100), 219 (M^+-C_2H_4, 28.3), 192 (M^+-C_2H_4-HCN, 13.2), 164 (13.7), 140 (8), 129 (18.4), 123 (M^{++}, 65.5), 102 (59), 90 (63.7), 77 (36.8), 63 (71), 51 (50), 39 (69.3).

6- Propyl benzimidazo[1,2-*c*]quinazoline (4d): Colorless needles (from benzene/ heptane); mp = 111-112 °C. Calculated for $C_{17}H_{15}N_3$; C 78.13, H 5.78, N 16.02 %. Found; C 78.3, H 5.7, N 16.01 %. IR (cm^{-1}); 1624, 1598, 1527, 1461, 1433, 772, 740. ^{1}H-nmr δ(ppm); 8.68 (dd, 1 H, J 6.3 Hz and 1.75 Hz, C_1-H), 8.05-7 (m, 7 H), 3.22 (t, 2 H, J 7.7 Hz, CH_2), 1.95 (m, 2 H, CH_2), 1.13 (t, 2 H, J 6.5 Hz, CH_3). ^{13}C-nmr δ(ppm); 149.16, 146.47, 143.21, 141.05, 127.74, 116.99 (6 C), 130.34, 126.56, 126.27, 124.07,122.93, 121.67, 118.94, 113.16 (8 CH), 36.60, 18.04 (2 CH_2), 13.11 (CH_3). MS m/z (%); 261 (M^+, 65), 246 (M^+-CH_3, 38), 233

(M^+-C_2H_4, 100), 219 (M^+-C_3H_6, 21.4), 207 (7), 192 (11.2), 164 (6), 131 (M^{++}, 6), 123 (10.2), 102 (12.2), 90 (12.2), 77 (12), 63 (13), 51 (10), 39 (16.3).

6-Buthyl benzimidazo[1,2-*c*]quinazoline (4e): Colorless crystals (from benzene / heptane); mp = 142 °C. Calculated for $C_{18}H_{17}N_3$; C 78.52, H 6.22, N 15.26 %. Found; C 78.6, H 6.2, N 15.3 %. IR (cm^{-1}); 1621, 1603, 1524, 1459, 1448, 1428, 775, 738. ^{1}H-nmr δ(ppm); 8.65 (dd, 1 H, J 6.5 Hz and 1.6 Hz, C_1-H), 8.1-7.2 (m, 7 H), 3.17 (t, 2 H, J 7.4 Hz, CH_2), 2.2-1.4 (m, 4H, 2 CH_2), 1.04 (t, 3 H, J 6.2 Hz, CH_3). ^{13}C-nmr δ(ppm); 150.42, 147.57, 144.11, 141.95, 128.68, 117.85 (6 C), 131.28, 127.33, 127.21, 125.05, 123.83, 122.65, 119.88, 114.02 (8 CH), 35.47, 27.57, 22.44 (3 CH_2), 13.97 (CH_3). MS m/z (%); 275 (M^+, 16.3), 260 (M^+-CH_3, 8.16), 246 (M^+-C_2H_5, 19.4), 233 (M^+-C_3H_6, 100), 219 (M^+-C_4H_8, 6), 207 (5), 192 (7), 164 (5), 138 (M^{++}, 4), 129 (6.1), 123 (10.2), 117 (6.2), 102 (12.2), 90 (10.2), 77 (10.2), 63 (9.2), 51 (6), 39 (10.2).

6-Phenyl benzimidazo[1,2-*c*]quinazoline (4f): Colorless needles (from ethanol); mp = 242 °C, lit.[8,9] mp = 240-242 °C. IR (cm^{-1}); 1621, 1585, 1529, 1457, 1439, 773, 741, 732. ^{1}H-nmr δ(ppm); 8.75 (dd, 1 H, J 6.9 Hz and 2.5 Hz, C_1-H), 8.1-7.0 (m, 11 H), 6.65 (d br, 1 H, J 8.2 Hz, C_8-H). MS m/z (%); 295 (M^+, 100), 192 (M^+-PhCN, 6.1), 164 (10.3), 147 (M^{++}, 53.6), 102 (16.5), 91 (6.2), 77 (12.3), 63 (15.5), 51 (12.4), 39 (10.3).

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