Regioselective Three-component Synthesis of Tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-ones

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Abstract - Reaction between 2-aminobenzimidazole **1**, dimedone **2** and aldehydes **3** in ethanol afforded tetracyclic 12-aryl-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-ones **4a-g** in good yields. The reactions were highly regioselective, what was established by nmr measurements.

INTRODUCTION

Varied biological activities have been attributed to quinazoline compounds, including analgesic, antiinflamatory, antipyretic,[1-3] antimicrobial,[4] anticonvulsant,[5] fungicidal,[6] antidepressant or other central nervous system affecting activities,[7] neoplasm inhibitors,virucides,[8] and recently two original benzimidazoquinazoline dimers were described as a new class of potent antitumour compounds.[9]

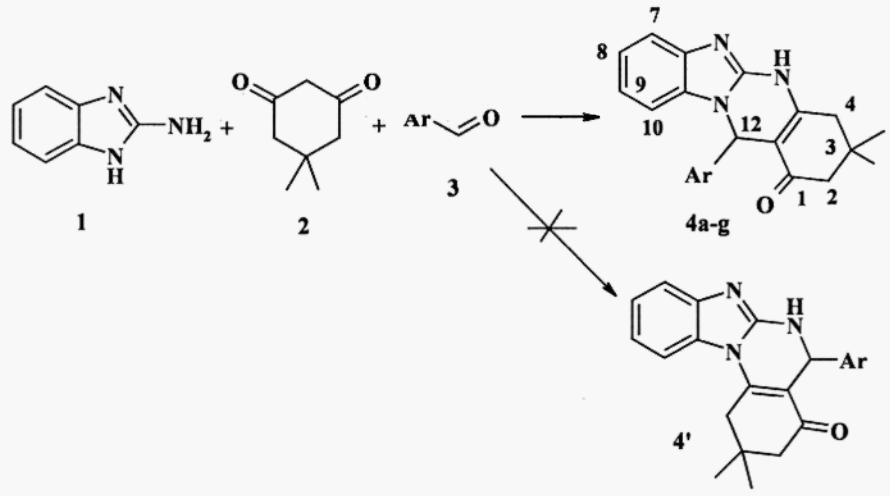
Cyclocondensation reactions are powerful synthetic methods, and even one of the most valuable for the preparation of heterocyclic compounds. Furthermore, multi-component condensations (MCC's) constitute an specially attractive synthetic strategy because permit the rapid an efficient generation of libraries in a single step and with great diversity of products simply modifying the reacting components.[10] We have recently reported an efficient method for synthesis of fused heterocyclic compounds containing nitrogen, by MCC's of heterocyclic amines, methylene active compounds and aldehydes.[11] In our continuous searching for novel polyheterocyclic systems with new potential pharmacological values,[12] we here report the preparation of the new tetracyclic benzimidazoquinazolines **4** from 2-aminobenzimidazole **1**.

RESULTS AND DISCUSSION

Accordingly, the synthesis of new benzimidazo[2,1-b]quinazolin-1(2*H*)-ones **4a-g** were achieved by reaction of 2-aminobenzimidazole **1**, dimedone **2** and aldehydes **3** in refluxing ethanol for 15-90 min and easily isolated in moderate to good yields (60-86 %) (Scheme 1).

This one-step cyclocondensation reaction could also afford the other regioisomeric products **4'** but, as observed on tlc, the reaction gave just a single product, what confirms that the reaction proceeds regiospecifically in favor of isomer type **4**. Compounds **4a-g** were characterized by spectroscopic (nmr, ms, uv) and analitical methods as 12-aryl-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-ones. The main support to distinguish between **4** and **4'** was provided from the nmr spectra (in particular HSQC, HMBC and NOESY experiments).

Concerning to ^{1}H-nmr spectra (see Table 1) the two relatively sharp singlets appear at arround 10.65-11-30 and 6.34-6.61 ppm with integrals in the ratio 1:1, which correspond to 5-NH-group (solvent exchangeable proton) and H-12, what along with no correlation between them in COSY preclude form **4'**.



Comp.	4a	4b	4c	4d	4e	4f	4g
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	3,4,5-tri$CH_3OC_6H_2$	4-ClC_6H_4	4-BrC_6H_4	4-$O_2NC_6H_4$
Yield	64	78	70	75	66	68	86

Scheme 1

TABLE 1. ^{1}H-NMR data for compounds **4a-g** (δ values, TMS as the Internal Standard, in DMSO-d_6)

Comp	3-CH_3 (two s)	NH (brs)	2-Ha (d)$^+$	2-Hb (d)$^+$	4-Ha (d)$^+$	4-Hb (d)$^+$	7-H (d)	8-H (dt)	9-H (dt)	10-H (d)	12-H (s)	2-Ar H_{orto} (d)	2-Ar H_{meta} (d)
4a	0.95, 1.07	10.68	2.08	2.23	2.54	2.61	7.35	7.03	6.93	7.16	6.39	7.13-7.30	
4b^{++}	0.95,1.06	10.65	2.07	2.23	2.53	2.60	7.34	7.03	6.90	7.16	6.34	7.16	7.01
4c^{++}	0.95, 1.06	11.10	2.11	2.26	2.58	2.66	7.37	7.05	6.96	7.26	6.36	7.26	6.79
4d^{++}	1.00, 1.08	10.90	2.11	2.28	2.60	2.70	7.42	7.06	7.00	7.37	6.36	6.64*	---
4e	0.94, 1.06	10.70	2.09	2.25	2.56	2.64	7.37	7.06	6.95	7.16	6.41	7.50	7.94
4f	0.95, 1.06	10.75	2.08	2.24	2.53	2.61	7.37	7.04	6.93	7.15	6.39	7.24	7.40
4g	0.92, 1.07	11.30	2.07	2.28	2.54	2.66	7.41	7.08	6.97	7.23	6.61	7.40	8.13

* Singlet

$^+$ $J_{2Ha\text{-}Hb}$ and $J_{4Ha\text{-}Hb}$ = 16.15±0.2 and 17.08±0.2 Hz respectively.

$^{++}$ CH_3 for **4b**, **4c** and **4d** at 2.18, 3.65 and 3.59/3.68 ppm respectively.

^{13}C-nmr spectra (with DEPT-135 experiment) permitted the assignation of signals belonging to quaternary, tertiary, secondary and primary carbon atoms for compounds **4a-g** (see Table 2).

The whole assignment of signals from both ^{1}H- and ^{13}C-nmr spectra of compounds **4a-g** was deduced from the concerted application 2D-nmr experiments, HSQC, HMBC and COSY, what confirmed the preferred tautomeric form as 2*H* for compounds **4**. Additional information coming from NOESY experiment precludes the possible structure of compounds **4'**. The NOE correlations between signals H-10H_{orto} and H-10H-12 for compounds **4** confirmed the structure assigned for compounds **4**. All of these evidences mentioned above ensure that the reaction route proceeds as indicated (i.e., **1** + **2** + **3** → **4**), discarding the possible formation of the isomeric compounds **4'**. Structures as **4'** were previously obtained by Strackov *et al* in the reaction of 2-formyldimedone and 2-aminobenzimidazole.[15]

TABLE 2. ^{13}C NMR chemical shifts (δ in ppm) for compounds **4a-g**

Comp.	4a	4b	4c	4d	4e	4f	4g
C-1	192.3	192.3	192.5	192.5	192.4	192.3	192.5
C-2	50.4	50.4	49.8	50.1	50.2	50.5	49.7
C-3	32.1	32.1	32.2	32.1	32.1	32.2	32.2
C-4	40.4	40.4	39.6	40.0	40.0	40.3	39.7
C-4a	150.4	150.2	149.9	150.5	150.6	150.7	150.9
C-5a	142.1	142.1	145.3	142.0	142.0	142.1	144.9
C-6a	141.6	145.8	141.9	145.4	140.5	141.0	141.8
C-7	116.9	116.9	116.8	116.9	117.0	117.0	117.1
C-8	121.8	121.7	121.6	121.7	121.9	122.0	122.0
C-9	120.4	120.4	120.3	120.4	120.5	120.6	120.7
C-10	109.8	109.8	110.0	110.2	109.8	109.8	109.8
C-10a	132.2	132.2	131.8	132.0	131.0	132.2	131.6
C-12	54.4	54.2	53.4	54.1	53.8	54.1	53.1
C12a	106.7	106.8	106.4	106.3	106.1	106.4	105.1
C_i	145.8	138.7	133.6	137.0	145.5	145.8	148.4
C_o	126.9	126.8	113.5	105.1	128.7	131.2	128.3
C_m	128.2	128.8	128.1	152.7	128.2	129.1	123.5
C_p	127.5	136.8	158.4	137.2	119.4	120.7	146.7
3-CH_3	26.9	26.9	26.5	26.5	26.9	27.1	26.6
	28.6	28.6	28.7	28.8	28.5	28.5	28.5

CH_3 for **4b** ,**4c** and **4d** at 20.4, 54.9 and 56.1 and 59.9 ppm respectively

In previous works,[11] on of heterocyclic amines, benzaldehydes and compounds with methylene active groups, we have also demonstrated that reactions present a high regioselectivities. Similarly, we assume for the initial step, a Knoevenagel condensation between **2** and **3** to form the benzylidenederivative of dimedone, which was isolated in some cases as a by-product, This intermediate suffers a Michael addition of the endocyclic nitrogen of **1** to the C=C bond of benzylidenederivative. The Michael adduct undergoes then cyclization with loss of one water molecule to render the isolated compounds **4**. In order to confirm the above, we made theoretical studies[16] on compound **1**, to determinate the contribution to HOMO of each nitrogen atom involved in the second step. We have found that the imino nitrogen contributes in a 15.8%, while the 2-amino nitrogen only ca 1% to orbital HOMO.[17] This confirms that the endocyclic nitrogen is more nucleophilic than the amino group. Formation of Michael adducts as intermediate in the reaction of 2-aminobenzimidazole and α,β-unsaturated compounds has also been described in various works.[18]

CONCLUSIONS

We have described in this paper the regioselective one-step three-component preparation of 12-aryl-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-ones from the reaction of 2-aminobenzimidazole, dimedone and benzaldehydes. The orientation of the reaction was determined in the basis of nmr spectroscopy The results demonstrate the versatility and high regioselectivity of this process.

EXPERIMENTAL

All melting points were taken on a Buchi melting point apparatus and are uncorrected. The ^1H- and ^{13}C nmr spectra were run on a Bruker AVANCE DPX 300 spectrometer in DMSO-d_6, and TMS as internal reference The mass spectra were recorded on a Fisons-Platform interface APCI in MeOH. The elemental analysis has been obtained using a LECO CHNS-900 equipment.

General procedure for the preparartion of the 12-aryl-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-ones 4a-g.
A solution of 2-aminobenzimidazole (**1**) (1 mmol), dimedone (**2**) (1 mmol) and benzaldehydes (**3**) (1 mmol) in 15 ml of absolute ethanol was heated to reflux for 15-90 minutes (tlc control). A precipitate is formed, which was isolated by filtration, washed with ethanol, dried and finally recrystallized from ethanol.

3,3-Dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-one 4a. This compound was obtained according to the general procedure as white crystals. M.p. 368 °C, yield 64 %. The mass spectrum shows the following peaks: Ms: (IE, 70 eV) m/z (%) = 344 (18), 343 (60, M^+), 267 (18), 266 (100, M^+-C_6H_5), 182 (10).
Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.97; H, 6.12; N, 12.24. Found: C, 76.93; H, 6.19; N, 12.17.

3,3-Dimethyl-12-(4-methylphenyl)-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-one 4b. This compound was obtained according to the general procedure as white crystals. M.p. 359 °C, yield 78 %. The mass spectrum shows the following peaks: Ms: (IE, 70 eV) m/z (%) = 358 (21), 357 (81, M^+), 266 (100, M^+-4-$CH_3C_6H_4$).
Anal. Calcd. for $C_{23}H_{23}N_3O$: C, 77.31; H, 6.44; N, 11.76. Found: C, 77.35; H, 6.38; N, 11.69.

12-(4-Methoxyphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-one 4c. This compound was obtained according to the general procedure as white crystals. M.p. 389 °C, yield 70 %. The mass spectrum shows the following peaks: Ms: (IE, 70 eV) m/z (%) = 374 (24), 373 (87, M^+), 372 (12), 267 (21), 266 (100, M^+-[4-$CH_3OC_6H_4$]), 265 (10), 182 (13).
Anal. Calcd. for $C_{23}H_{23}N_3O_2$: C, 73.99; H, 6.17; N, 11.26. Found: C, 73.91; H, 6.12; N, 11.29.

12-(3,4,5-Trimethoxyphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-one 4d. This compound was obtained according to the general procedure as white crystals. M.p. 328 °C, yield 75 %. The mass spectrum shows the following peaks: Ms: (IE, 70 eV) m/z (%) = 434 (31), 433 (100, M^+), 267 (15), 266 (73, M^+-3,4,5-$(CH_3O)_3C_6H_2$).
Anal. Calcd. for $C_{25}H_{27}N_3O_4$: C, 69.28; H, 6.23; N, 9.70. Found: C, 69.33; H, 6.27; N, 9.62.

12-(4-Chlorophenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-one 4e. This compound was obtained according to the general procedure as white crystals. M.p. 393 °C, yield 60 %. The mass spectrum shows the following peaks: : (70 eV) m/z (%) = 379/377 (10/26, M^+), 266 (100, M^+-4-ClC_6H_4), 182 (14), 159 (13), 133 (54), 106 (12), 105 (20), 90 (20), 83 (21), 79 (15), 78 (22), 77 (34), 76 (14), 75 (24), 66 (18), 65 (20), 64 (24), 63 (29), 57 (13), 56 (17), 55 (39), 53 (23), 52 (27), 51 (41), 44 (67), 43 (45).
Anal. Calcd. for $C_{22}H_{20}ClN_3O$: C, 69.93; H, 5.30; N, 11.12. Found: C, 69.97; H, 5.23; N, 11.19.

12-(4-Bromophenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-one 4f. This compound was obtained according to the general procedure as white crystals. M.p. 369 °C, yield 68 %. The mass spectrum shows the following peaks: Ms: (IE, 70 eV) m/z (%) = 423/421 (33/32, M^+), 266 (100, M^+-4-BrC_6H_4).
Anal. Calcd. for $C_{22}H_{20}BrN_3O$: C, 62.56; H, 4.74; N, 9.95. Found: C, 62.62; H, 4.68; N, 9.98.

3,3-Dimethyl-12-(4-nitrophenyl)-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2*H*)-one 4g. This compound was obtained according to the general procedure as yellow crystals. M.p. 355 °C, yield 86 %. The mass spectrum shows the following peaks: Ms: (IE, 70 eV) m/z (%) = 389 (18), 388 (68, M^+), 267 (21), 266 (100, M^+-4-$O_2NC_6H_4$), 182 (12).
Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.04; H, 5.15; N, 14.43. Found: C, 68.10; H, 5.11; N, 14.37.

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REFERENCES AND NOTES

1. G. Daidone, B. Maggio, D. Raffa, S. Plescia, M. L. Bajardi, A. Caruso, V. M. C. Cuttuli and M. Amico-Roxas, *Eur. J. Med. Chem.*, **29**, 707 (1994).

2. A. A. Backhit and M. A. Khalíl, *Pharmazie*, **53**, 539 (1998).

3. R. Argarwal, C. Singli and N. S. Mishara, *Ind. Drugs*, **25**, 185 (1988).

4. B. Pramella, E. Rajanarender and A. K. Murty, *Ind. J. Heterocyclic Chem.*, **2**, 115 (1992).

5. M. Shyimad, R. Kalsi, K. S. Dixit and J. P. Barthwal, *Arzeim-Forsch. Drug Res.*, **41**, 514 (1991).

6. Kh. M. Shakhidoyator, E. O. Eripor, L. M. Yun, M. Yamankulov and Ch. Kadyrov, *Fungitsidy*, 66 (1980); *Chem. Abstr.*: **94**, 192253 (1981).

7. J. Fetter, T. Czuppon, G. Hornyak and A. Feller, *Tetrahedron*, **34**, 247 (1997).

8. B. M. Fernandez, J. M. Castellano, M. C. Redondo, E. Schlick and G. Kreilhauer, Eur. Pat. Appl. EP 331,093 (CI. C071D487/04) 1989.

9. M. F. Brana and M. J. Perez, *J. Heterocyclic Chem.*, **34**, 807 (1997).

10. (a) R. S. Varma and D. Kumar, *Tetrahedron Lett.*, **40**, 7665 (1999). (b) K. Groebke, L. Weber and F. Mehlin, *Synlett,*, 661 (1998). (c) C. O. Kappe, D. Kumar, D. and R. S. Varma, *Synthesis*, 1799 (1999).

11. a) J. Quiroga, C. Cisneros, B. Insuasty, R. Abonía, M. Nogueras and A. Sánchez, *Tetrahedron Lett.*, **42**, 5625 (2001); b) J. Quiroga, D. Mejía, B. Insuasty, R. Abonía, M. Nogueras, A. Sánchez, J. Cobo and J. N. Low, *Tetrahedron.*, **57**, 6947 (2001); c) J. Quiroga, S. Cruz, B. Insuasty, R. Abonía, M. Nogueras, A. Sánchez, J. Cobo and J. N. Low, *J. Heterocyclic Chem.*, **38**, 53 (2001); d) J. Quiroga, S. Cruz, B. Insuasty and R. Abonía, *Heterocyclic Commun.*, **6** (3), 275 (2000); e) J. Quiroga, M. Alvarado, B. Insuasty, M. Nogueras, A. Sánchez and M. D. López, *J. Heterocyclic Chem.*, **36**, 113 (1999).

12. a) T. Besson, J. Guillard and C. W. Rees, *Tetrahedron Lett.*, **41**, 1027 (2000); (b) T. Besson and J. Guillard, *Tetrahedron*, **55**, 5139 (1999); (c) C. Comoy, V. Guerin, B. Pfeiffer, M. C. Rettori, P. Renard and G. Guillaumet, *Bioorg. Med. Chem.*, **8**, 483 (2000).

13. A. Bax and S. Subramanían, *J. Magn. Reson.*, **65**, 565 (1986).

14. A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, **108**, 2093 (1986).

15. A. Ya Strakov, M.V. Petrova, Y. Popelis, A.A. Krasnova, I.A. Strakova, *Khim. Geterosikl. Soedin.*, (2), 247 (1996).

16. PM3 Method in Spartan Ver 5.0, Wavefunction Inc.

17. The porcentual contributions were calculated from the addition of the square of the contribution of p_x, p_y and p_z orbitals on the nitrogen atom.

18. a) V. A. Anisimova, A. M. Simonov and A. F. Pozharskii, *Khim. Geterosikl. Soedin.*, 797 (1973); b) A. J. Elliott, H. Guzyk and J. R. Soler, *J. Heterocyclic Chem.*, **19,** 1437 (1982); c) E. I. Al-Afaleq, *Synth. Commun.*, **30**, 1985 (2000).

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