This article was downloaded by: [Brown University]
On: 07 September 2012, At: 06:16
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of 1-Amino[1,3,5]triazino[1,2a]-benzimidazolo-2-one and Pyrimidino[1,2a]benzimidazolo-4-one Derivatives

Azhar Hajri [a] & Raoudha Abderrahim [a]

[a] Laboratory of Lamellaires Materials and Hybrids Nanomaterials, University of Carthage, Faculty of Science of Bizerte, Bizerte, Tunisia

Version of record first published: 29 Jun 2011

To cite this article: Azhar Hajri & Raoudha Abderrahim (2011): Facile Synthesis of 1-Amino[1,3,5]triazino[1,2a]-benzimidazolo-2-one and Pyrimidino[1,2a]benzimidazolo-4-one Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:19, 2920-2926

To link to this article: http://dx.doi.org/10.1080/00397911.2010.515366

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings,

demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Downloaded by [Brown University] at 06:16 07 September 2012

Synthetic Communications®, 41: 2920–2926, 2011
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.515366

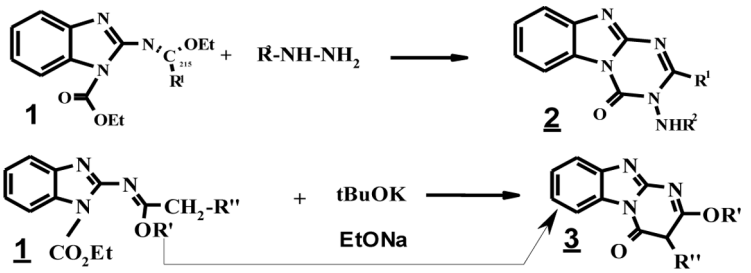
Downloaded by [Brown University] at 06:16 07 September 2012

FACILE SYNTHESIS OF 1-AMINO[1,3,5]-TRIAZINO[1,2a]BENZIMIDAZOLO-2-ONE AND PYRIMIDINO[1,2a]BENZIMIDAZOLO-4-ONE DERIVATIVES

Azhar Hajri and Raoudha Abderrahim

Laboratory of Lamellaires Materials and Hybrids Nanomaterials, University of Carthage, Faculty of Science of Bizerte, Bizerte, Tunisia

GRAPHICAL ABSTRACT



Abstract *N-(1-Carboethoxy-benzimidazol-2-yl)* ***1*** *reacted with different hydrazines to give [1,3,5]triazino[1,2a]benzimidazole derivatives* ***2****. Treatment of compound* ***1*** *with tBuOK and EtONa yielded pyrimidino[1,2a]benzimidazole derivatives* ***3*** *in good yields.*

Keywords Hydrazine; N-2(1-carboethoxy-benzimidazol-2-yl); pyrimidino[1,2a]benzimidazole; [1,3,5]triazino[1,2a]benzimidazole

INTRODUCTION

We are currently interested in developing routes for the synthesis of a new family of substituted benzimidazoles because of their pharmacological activity. Furthermore, many condensed heterocyclic systems, especially when linked to a pyrimidine ring, play important roles in analgesic and anti-inflammatory drugs and have antimicrobial activities.[1,2] Many of them are widely used as antidepressive[3] and antiviral drugs.[4] Some heterocycles containing pyrimidine moieties were reportedly used as antagonists at the A_1 adenosine receptor (A_1AR)[5] and in antitumor drugs.[6]

Pyrimidino[1,2-a]benzimidazoles have been found to have significant analgesic and anti-inflammatory,[7] antiproliferative,[8] anticancer,[9] and macrofilaricidal

Received May 27, 2010.

Address correspondence to Raoudha Abderrahim, Laboratory of Lamellaires Materials and Hybrids Nanomaterials, University of Carthage, Faculty of Science of Bizerte, 7021 Jarzouna, Bizerte, Tunisia. E-mail: Abderrahim_raoudha@yahoo.fr

Downloaded by [Brown University] at 06:16 07 September 2012

effects,[10] and they act as diuretics.[11] [1,3,5]Triazinobenzimidazole derivatives have a very interesting heterocyclic ring system because of their wide range of pharmacological applications.

A variety of biological[12] effects have been attributed to the heterocyclic nucleus *s*-triazino[1,2-*a*]benzimidazole; in particular, amino-[1,3,5]triazino[1,2-*a*]-benzimidazoles have been found to possess both antibacterial[13] and dihydrofolate reductase (DHFR) inhibitory effects of malarial plasmodium,[14] They are used to treat parasitic[15] infections and as anticancer,[16] and antitubercular agents.[17] In continuation of our recent work on the synthesis of fused heterocycles containing the triazine or pyrimidine ring,[18–20] we herein describe an efficient route to the synthesis of triazino benzimidazole and pyrimido benzimidazole in good yields.

The methodology was based on the reaction of N-ethoxycarbonyl iminoesters **1** with different hydrazines to give triazino benzimidazole, and treatment of **1** with tBuOK or EtONa afforded pyrimidino benzimidazole.

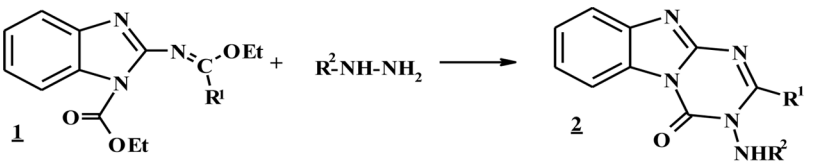
RESULTS AND DISCUSSION

N-Ethoxycarbonyl iminoesters **1** were obtained by the reaction of iminoethers derived from 2-aminobenzimidazole with ethyl chloroformate.[21,22]

Treatment of N-ethoxycarbonyl iminoester **1** with hydrazine derivatives under reflux of ethanol afforded benzimidazolo-triazine **2** (Scheme 1). The results obtained from elemental analysis, infrared (IR), ^{1}H NMR, and ^{13}C NMR data as well as the mass spectra are in agreement with the assigned structures **2**. The IR spectrum of **2** showed absorption bands at 1701 cm^{-1} (C=O) and 1630 cm^{-1} (C=N) and a new absorption band at around 3220–3331 cm^{-1} attributed to NH_2 (if hydrazine hydrate).

The ^{1}H NMR spectrum of compound **2** revealed the disappearance of a signal specific to the ethoxy group and the presence of methyl or phenyl groups introduced by hydrazine. The ^{13}C NMR revealed the signal of the different carbons and confirmed the formation of **2**.

From a mechanistic viewpoint, there is no indication whatsoever of initial attack of the hydrazine group on the carbon of iminoether or on the carbon of carbamate. We may consider that the cyclization process occurs throughout the



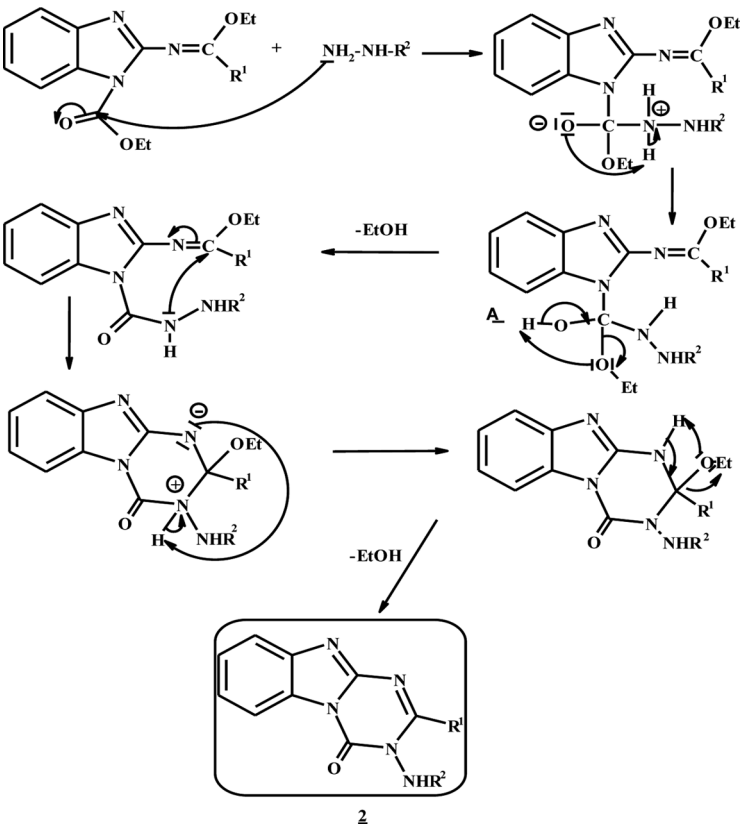
	2a	2b	2c	2d	2e	2f
R^1	Me	Et	Me	Et	Me	Et
R^2	Ph	Ph	H	H	Me	Me

Scheme 1. Synthesis of **2**.

formation of intermediate **A**, because the carbon of carbamate was more electrophilic than the carbon of the iminoether group.[23] The attack on the carbon of carbamate by the nitrogen atom of hydrazine forms intermediate **A**, which cannot be isolated. The latter undergoes intramolecular nucleophilic cyclization to give benzimidazolo triazine **2** (Scheme 2).

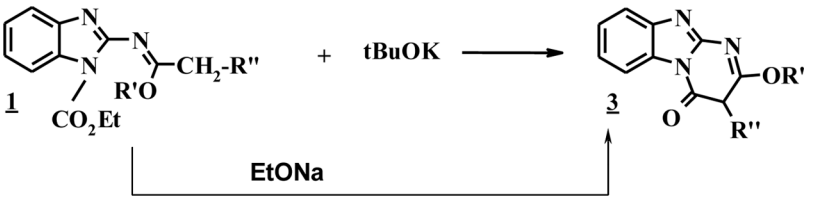
On the other hand, the reaction of N-ethoxycarbonyl iminoesters **1** with tBuOK in anhydrous tetrahydrofuran (THF) at 0 °C under reflux of nitrogen leads to pyrimido[1,2a]benzimidazole derivatives **3**. Compound **3** was also independently synthesized through another pathway via the condensation of EtONa with the N-ethoxycarbonyl iminoesters **1**. The structures of compounds **3a–c** were established on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR).

The reaction of compound **1** with tBuOK or EtONa yielded pyrimido benzimidazoles **3** in good yields (Scheme 3). When the base was EtONa, the compounds **3a–c** were obtained in better yield than when we employed the tBuOK. The results obtained from elemental analysis of some products and the IR, ^{1}H NMR, and ^{13}C NMR data are in agreement with the assigned structures **3**. The ^{1}H NMR and ^{13}C NMR spectra of compound **3** are consistent with the presence of one isomer.



Scheme 2. Proposed mechanism of synthesis of **2**.

Downloaded by [Brown University] at 06:16 07 September 2012



3a R' = Me R'' = H
3b R' = Et R'' = H
3c R' = Et R'' = Me

Scheme 3. Synthesis reaction of compound **3**.

The methyl and hydrogen regions of the ^{1}H NMR spectrum of **3c** exhibit one doublet for CH_3 and one quadruplet for H. This is confirmed by ^{13}C NMR spectrum of compound **3c**, which shows a singlet at 11.21 ppm and singlet at 44.31 ppm assigned respectively to the carbon of CH_3 and to the carbon of CH of the new stereocenter.

The IR absorption spectrum of compound **3** was characterized by the presence of a band at 1710 cm^{-1} for C=O group, as well as intense stretching bands for C=N at 1615 cm^{-1} and C=C at 1600 cm^{-1}. ^{1}H NMR of **3** exhibited a multiplet for the aromatic protons around 7.5 ppm, the disappearance of the sharp line of one ethoxy peak, and the presence of the peak of ethoxy or methoxy protons.^{13}C NMR spectrum was consistent with the proposed structures and showed the absence of the carbon peaks of ethoxy and methoxy groups.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Paragon 1000 PC spectrometer in $CHCl_3$ solution.^{1}H and ^{13}C NMR spectra were recorded with $(CD_3)_2SO$ or $CDCl_3$ solvent containing tetramethylsilane (TMS) on a Bruker 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75.47 MHz). The chemical shifts (δ) are reported in ppm relative to TMS (internal reference). For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet.

Melting points were obtained using a Büchi melting-point apparatus and are uncorrected. Elemental microanalysis was performed on a Perkin-Elmer CHN-2400 analyzer apparatus.

Mass spectra was recorded on a HP-5890 A using the impact mode (70 eV).

N-Ethoxycarbonyl Iminoesters 1

Ethyl chloroformate (0.11 mol) was added dropwise to a mixture of iminoester (0.11 mmol) (iminoester was obtained by condensation of 2-aminobenzimidazole with an excess of orthester) and 0.12 mol of pyridine in 50 mL of anhydrous ether at 0 °C. The mixture was stirred for 3 h. The pyridinium chlorhydrate obtained was filtered. The solvent was removed under vacuum, and the resulting solid was filtered off and dried.

Downloaded by [Brown University] at 06:16 07 September 2012

Compound 1a. Yield: 65%, mp: 165 °C. IR ($CHCl_3$, ν (cm^{-1}): $\nu = 1750$ (C=O), $\nu = 1670$ (C=N). ^1H NMR ($CDCl_3$): δ 4.50 (q, 4H, CH_2-), 1.40 (s, 3H, CH_3), 1.50 (t, 6H, $2CH_3$), 7.30 (m, 4H, H_{arom}).

Compound 1b. Yield: 70%, mp: 65 °C. IR ($CHCl_3$, ν (cm^{-1}): $\nu = 1750$ (C=O), $\nu = 1670$ (C=N). ^1H NMR ($CDCl_3$): δ 4.50 (q, 4H, CH_2-), 1.40 (t, 9H, $3CH_3$), 2.50 (q, 2H, CH_2), 7.30 (m, 4H, H_{arom}).

[1,3,5]Triazino[1, 2-a]benzimidazole 2

Hydrazine (2.1 mmol) was added to a solution of imidate **1** (2 mmol) in ethanol (10 mL). The reaction mixture was stirred and heated under reflux for 48 h. The solvent was removed under vacuum, and the resulting solid was filtered off, dried and crystallized.

Compound 2a. Yield: 65%, mp: 218 °C. IR ($CHCl_3$, ν (cm^{-1}): $\nu = 1701$ (C=O), $\nu = 1630$ (C=N). ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 7.10 (broad s, 1H, NH deuterium exchangeable), 6.76–7.43 (m, $9H_{arom}$).^{13}C NMR ($CDCl_3$): δ 13.87, 113.70, 115.15, 123.99, 129.70, 141.86, 151.02, 153.26. Calcd. for $C_{16}H_{13}N_5O$ (%): C, 65.97; H, 4.46; N, 24.05. Found (%): C, 65.90; H, 4.30; N, 23.95.

Compound 2b. Yield: 55%, mp: 210 °C. IR ($CHCl_3$, ν (cm^{-1}): $\nu = 1701$ (C=O), $\nu = 1630$ (C=N). ^1H NMR ($CDCl_3$): δ 1.36 (t, 3H, CH_3), 2.49 (q, 2H, CH_2), 7.15 (s, 1H, NH deuterium exchangeable), 6.93–7.58 (m, $9H_{arom}$). ^{13}C NMR ($CDCl_3$): δ 10.77, 21.62, 112.90, 115.45, 122.19, 129.70, 142.86, 150.02, 152.96.

Compound 2c. Yield: 52%, mp: 220 °C. IR ($CHCl_3$, ν (cm^{-1}): $\nu = 3310$–3231 (NH_2), $\nu = 1701$ (C=O), $\nu = 1630$ (C=N). ^1H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 6.76–7.50 (m, 6H, NH_2 deuterium exchangeable and $4H_{arom}$). ^{13}C NMR ($CDCl_3$): δ 13.21, 112.52, 121.24, 134.96, 149.75, 152.02, 153.71, 156.10. Calcd. for $C_{10}H_9N_5O$) (%): C, 55.81; H, 3.72; N, 32.55. Found (%): C, 55.83; H, 3.75; N, 32.57.

Compound 2d. Yield: 45%, mp: 222 °C. IR ($CHCl_3$, ν (cm^{-1}), $\nu = 3320$–3231 (NH_2), $\nu = 1701$ (C=O), $\nu = 1645$ (C=N). ^1H NMR ($CDCl_3$): δ 1.30 (t, 3H, CH_3), 2.70 (q, 2H, CH_2), 6.82–7.36 (m, 6H, NH_2 deuterium exchangeable and $4H_{arom}$). ^{13}C NMR ($CDCl_3$): δ 10.21, 23.42, 111.92, 120.28, 137.01, 150.05, 151.02, 154.71, 155.39. *M/s* (%): 229 (10), 200 (80), 170 (18), 158 (16), 133 (100), 105 (40), 90 (30), 78 (10).

Compound 2e. Yield: 65%, mp 240 °C. IR ($CHCl_3$, ν (cm^{-1}), $\nu = 3320$–3231 (NH_2), $\nu = 1701$(C=O), $\nu = 1645$ (C=N). ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 3.70 (s, 3H, NCH_3), 4.50 (s, 1H, NH deuterium exchangeable), 7.10 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 13.20, 37.22, 111.90, 116.21, 121.19, 131.70, 141.86, 150.22, 1523.01.

Compound 2f. Yield: 60%, mp 230 °C. ^1H NMR ($CDCl_3$): δ 1.41 (t, 3H, CH_3), 2.70 (q, 2H, CH_2), 3.50 (s, 3H, NCH_3), 4.80 (s, 1H, NH deuterium exchangeable), 7.10–7.55 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 11.00, 26.22, 37.15, 112.90, 116.01, 122.19, 128.70, 142.86, 150.02, 152.96. Calcd. for $C_{12}H_{13}N_5O$ (%): C, 59.29; H, 5.34; N, 28.64. Found (%): C, 59.26; H, 5.32; N, 28.67.

Downloaded by [Brown University] at 06:16 07 September 2012

Pyrimidino[1, 2-a]benzimidazole Derivatives 3

N-2-(1-Carbethoxybenzimidazol-2-yl) imidate **1** (5 mmol) in 30 mL of THF was added dropwise with stirring to a cooled THF solution of potassium *tert*-butoxide (7 mmol, tBuOK) in 10 mL THF at 0 °C under reflux of nitrogen. In a similar reaction, **1** reacted with 7 mmol of EtONa (0.16 g of Na added to 0.41 mL of EtOH dissolved in 20 mL of anhydrous diethyl ether). When all substrate **1** was added, the reaction mixture was allowed to reach room temperature and stirred for 24 h. The obtained solution was hydrolyzed with freshly prepared, NH_4Cl and extracted three times with 20 mL of diethyl ether. The organic extract was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the resulting solid was filtered off, dried, and crystallized from CCl_4.

Compound 3a. Yield: 73%, mp: 115 °C. IR ($CHCl_3$), ν (cm^{-1}), $\nu = 3030$ (CH_{arom}), 1615 (C=N), 1700 (C=O), 1600 (C=C). ^1H NMR ($CDCl_3$): δ 2.30 (s, 2H, O=C-C$\underline{H}_2$), 3.90 (s, 3H, O-C$\underline{H}_3$), 7.30 (mu, 4H, C$\underline{H}_{arom}$). ^{13}C NMR ($CDCl_3$): δ 45.30, 51.10, 113.00, 118.22, 121.01, 124.10, 132.30, 144.05, 148.20, 161.23, 169.15.

Compound 3b. Yield: 76%, mp: 148 °C. IR ($CHCl_3$), ν (cm^{-1}), $\nu = 3030$ (CH_{arom}), 1615 (C=N), 1700 (C=O), 1600 (C=C). ^1H NMR ($CDCl_3$): δ 2.30 (s, 2H, O=C-C$\underline{H}_2$), 1.31 (t, 3H, O-CH_2-C$\underline{H}_3$), 4.22 (q, 2H, O-C$\underline{H}_2$), 7.23 (mu, 4H, C$\underline{H}_{arom}$). ^{13}C NMR ($CDCl_3$) δ 14.03, 44.30, 59.20, 113.04, 119.25, 122.20, 124.51, 131.02, 143.22, 147.12, 161.00, 168.00. Anal. calcd. for $C_{11}H_{12}N_3O_2$ (%): C, 62.88; H, 4.8; N, 18.34. Found: C, 62.60; H, 4.71; N, 18.30.

Compound 3c. Yield: 70%, mp: 165 °C. IR ($CHCl_3$), ν (cm^{-1}), $\nu = 3030$ (CH_{arom}), 1615 (C=N), 1700 (C=O), 1600 (C=C). ^1H NMR ($CDCl_3$), δ 2.30 (q, 1H, CH), 1.11 (d, 3H, C$\underline{H}_3$), 1.20 (t, 3H, O-CH_2-C$\underline{H}_3$), 4.30 (q, H, CH_3-C$\underline{H}_2$-O), 7.22 (mu, 4H, C$\underline{H}_{arom}$). ^{13}C NMR ($CDCl_3$) δ 11.21, 14.00, 44.31, 64.02, 113.11, 119.20, 121.30, 124.00. 132.02, 144.10, 149.05, 163.01, 170.02. Anal. calcd. for $C_{12}H_{14}N_3O_2$ (%): C, 62.06; H, 6.03; N, 18.10. Found: C, 62.10; H, 5.98; N, 18.15.

REFERENCES

1. Gavrilov, M. Y.; Mardanova, L. G.; Kolla, V. E.; Konshin, M. E. Synthèses, anti-inflammatory and analgesic activities of 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carbo-xamides. *Pharm. Chem. J.* **1989**, *22*(7), 554–556.
2. Abdel-Rahman, B. A.; El-Gazzar, M.; El-Enany, M.; Mahmoud, N. M. Synthesis, analgesic, anti-inflammatory, and antimicrobial activity of some novel pyrimido[4,5-*b*]quinolin-4-ones. *Bioorg. Med. Chem.* **2008**, *16*(6), 3261–3273.
3. Bernier, J. L.; Henichart, J. P.; Warin, V.; Baert, T. Synthesis and structure–activity relation ship of a pyrimido[4,5-d]pyrimidine derivative with antidepressant activity. *J. Pharm. Sci.* **1980**, *69*(11), 1343–1345.
4. Dinan, F. J.; Bardos, T. J. Synthesis of some new S-alkylated derivatives of 5-mercapto-2′-deoxyuridine as potential antiviral agents. *J. Med. Chem.* **1980**, *23*(5), 569–572.
5. Settimo, F. D.; Primofiore, G.; Taliani, S.; Marini, A. M.; La Motta, C.; Novellino, E.; Greco, G.; Lavecchia, A.; Trincavelli, L.; Martini, C. 3-Aryl[1,2,4]triazino[4,3-*a*]benzimidazol-4(10*H*)-ones: A new class of selective A_1 adenosine receptor antagonists. *J. Med. Chem.* **2001**, *44*(3), 316–327.

Downloaded by [Brown University] at 06:16 07 September 2012

6. Said, M.; Abouzid, K.; Mouneer, A.; Ahmedy, A.; Osman, A. M. Synthesis and biological evaluation of new thiazolopyrimidines. *Arch. Pharm. Res.* **2004**, *27*(5), 471–477.
7. Shaaban, M. R.; Saleh, T. S.; Mayhoub, A. S.; Mansour, A.; Farag, A. M. Synthesis and analgesic/anti-inflammatory evaluation of fused heterocyclic ring systems incorporating phenylsulfonyl moiety. *Bioorg. Med. Chem.* **2008**, *16*, 6344–6352.
8. Nawrocka, W.; Sztuba, B.; Kowalska, M. W.; Liszkiewicz, H.; Wietrzyk, J.; Nasulewicz, A.; Pelczynska, M.; Opolski, A. Synthesis and antiproliferative activity in vitro of 2-aminobenzimidazole derivatives. *Farmaco* **2004**, *59*(2), 83–91.
9. Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1. *Bioorg. Med. Chem.* **2002**, *10*, 3997–4004.
10. Ojha, V.; Singh, J.; Bhakuni, D. S.; Singh, S.; Chatterjee, R. K. Synthesis of 5-substituted 2-carbalkoxyamino-1H-benximidazoles as possible microfilaricida agents. *Indian J. Chem.* **1991**, *30B*, 324–326.
11. Wahe, H.; Asobo, P. F.; Cherkasov, R. A.; Nkengfack, A. E.; Folefoc, G. N.; Fomum, Z. T.; Doepp, D. Heterocycles of biological importance, part 6: The formation of novel biologically active pyrimido[1,2a]benzimidazoles from electron-deficient alkynes and 2-aminobenzimidazoles. *Arkivoc* **2003**, *14*, 170.
12. Dolzhenko, A. V.; Chui, W. K.; Dolzhenko, A. V.; Chan, L. W. Synthesis and biological activity of fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles. *J. Fluorine Chem.* **2005**, *126*(5), 759–763.
13. Gulyas, G.; Emri, T.; Simon, A.; Gyorgydeak, Z. In vitro antimicrobial activity of 3,4-dihydro-s-triazinobenzimidazole derivatives. *Folia Microbiol.* **2002**, *47*, 29–31.
14. Toyoda, T.; Brobey, R. K. B.; Sano, G. I.; Horii, T.; Tomioka, N.; Itai, A. Lead discovery of inhibitors of the dihydrofolate reductase domain of *Plasmodium falciparum* dihydrofolate reductase–thymidylate synthase. *Biochem. Biophys. Res. Commun.* **1997**, *235*, 515–519.
15. Ridley, R. G. Chemotherapeutic hope on the horizon for *Plasmodium vivax* malaria. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*(21), 13362–13364.
16. Berman, E. M.; Werbel, L. M. The renewed potential for folate antagonists in contemporary cancer chemotherapy. *J. Med. Chem.* **1991**, *34*(2), 479–485.
17. Dolzhenko, A. V.; Chui, W.-K. Synthesis of 2-amino-*s*-triazino[1,2-*a*]benzimidazoles as potential antifolates from 2-guanidino- and 2-guanidino-5-methylbenzimidazoles. *J. Heterocyclic Chem.* **2006**, *43*(1), 95–100.
18. Hussein, M. B. G.; Abdel-Alim, M. A.; Hashem, A. A. M. Synthesis and antimicrobial activity of some new 1-alkyl-2-alkylthio-1,2,4-triazolobenzimidazole derivatives. *Arch. Pharm. Res.* **2006**, *29*(1), 26–33.
19. Abderrahim, R.; Hajjem, B.; Baccar, B. A convenient synthesis of [1,2-a]benzimidazo-1,3,5-triazin-4-thiones and [1,2-a]benzimidazo-1,3,5-triazin-4-ones. *J. Soc. Chim. Tunisie* **1994**, *3*, 423–426.
20. Raouafi, N.; Abderrahim, R.; Belhadj Amor, A.; Boujlel, K.; Ben Khoud, M. L. Reactivité des N-benzimidazoyl imidate en milieu basique: Synthèse de pyrimido[1,2a]benzimidazole. *J. Soc. Alg. Chim.* **2002**, *12*(2), 225–232.
21. Abderrahim, R.; Hajjem, B.; Zantour, H.; Baccar, B. Reaction of N-2-(1-carbethoxy)-and N-2-(1-acyl)-benzimidazoimidates with Grignard reagents: Synthesis of 1,3,5-oxadiazino-(1,2-a)benzimidazoles. *Synth. Commun.* **1997**, *27*, 3039–3046.
22. Abderrahim, R.; Medini, H.; Kossai, R.; Boujlel, K. Reduction of N-2-substituted benzimidazoyl imidates. *Synth. Commun*. **2002**, *32*(2), 241–245.
23. Abderrahim, R.; Baccar, B.; Ben Khoud, M. L. Synthèse de [1,2a]benzimidazolo-1,3,5,2-triazaphosphorine-2-oxydes. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2002**, *177*, 1033–1040.

Downloaded by [Brown University] at 06:16 07 September 2012