HETEROCYCLES, Vol. 57, No. 8, 2002, pp. 1423 - 1432, Received, 19th April, 2002

MICROWAVE ASSISTED SYNTHESIS OF NEW BENZIMIDAZOLES

Yves Njoya,[a,b] Narimène Boufatah,[a,b] Armand Gellis,[a,b] Pascal Rathelot,[a] Michel P. Crozet,[b] and Patrice Vanelle [a,b]*

[a]Department of Organic Chemistry, University of Mediterranée, Faculty of Pharmacy, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France

Fax: (33) 04 91 79 46 77; E-mail: patrice.vanelle@pharmacie.univ-mrs.fr

[b]LCMO, UMR 6517, CNRS-Universities of Aix-Marseille 1 and 3, BP 562, 13397 Marseille Cedex 20, France

Abstract – New potentially bioactive and highly functionalized benzimidazoles were synthesized by using microwave irradiation methodology in multi-steps: construction of benzimidazole ring, *N*-methylation and electron transfer *C*-alkylation (followed by base-promoted nitrous acid elimination) or *S*-alkylation.

Microwave irradiation and its applications for organic reactions is currently under extensive examination and has been recently reviewed.[1-6] Heterogeneous reactions facilitated by supported reagents on various solid inorganic surfaces such as SiO_2 have received attention in recent years because of the greater selectivity and simple reaction work-up.[7,8] Microwave heating has been used for the rapid synthesis of a variety of heterocyclic compounds both in solution phase as well as under solvent-free conditions.[9-14] The use of such microwave approach has several advantages such as short reaction times compared to conventional procedure, ease of work-up, reduction in the usual thermal degradation and formation of pure products in high yields. Further, the solventless microwave-assisted reactions are now gaining popularity as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development and with a possibility of scaling up the reactions on preparative scale.[15-18]

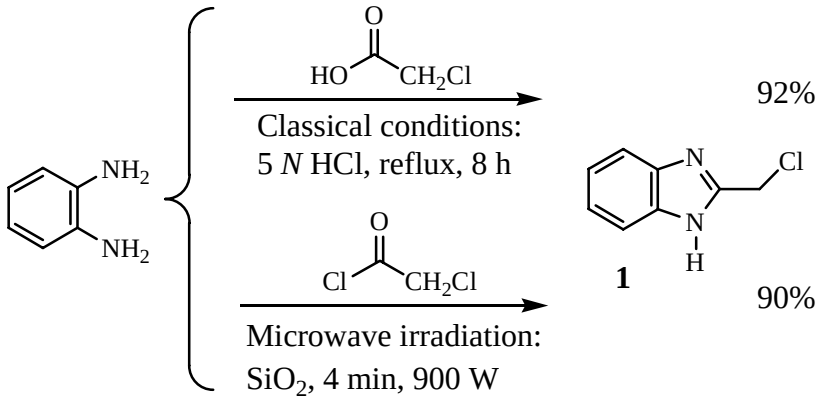
Compounds containing benzimidazole group have been shown to exhibit a broad spectrum of pharmacological activities.[19] Clinical examples include mebendazole, albendazole (anthelmintics),[20,21] astemizole (antihistamine),[22] and omeprazole (antiulcerative).[23] In addition, benzimidazole based compounds have shown such diverse biological activities as inhibition of phosphodiesterase IV[24] and antagonism of angiotensin 1[25,26] and neuropeptide Y[27] binding.

On the other hand, the single electron transfer reactions,[28-31] recently under microwave irradiation,[32-34] are one of the main research topics in our laboratories. As a part of our program to develop the synthesis of heterocyclic compounds under these conditions and to adapt heterocyclic methodologies to a high speed synthesis, we report here a microwave assisted preparation of new potentially bioactive benzimidazole derivatives.

2-Alkylbenzimidazoles were prepared by classical cyclocondensation of 1,2-arylenediamines with the corresponding aldehydes[35] or carboxylic acids.[11,36,37] Generally, the reaction time was 4 to 48 h and yield 30 to 65%.

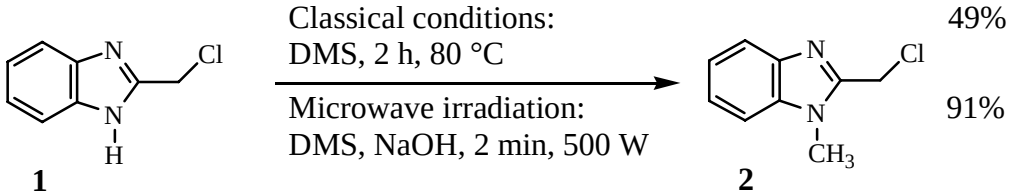
2-Chloromethyl-1*H*-benzimidazole (**1**) was obtained in 92% yield following the classical method (chloroacetic acid, 5 *N* HCl, refluxed for 8 h). Microwave irradiation is another potential strategy to realize this cycloaddition. In typical procedure (SiO_2, 500 W, 4 min), the chloride (**1**) was prepared in 90% yield from the condensation of chloroacetyl chloride with 1,2-phenylenediamine. The reaction rate was accelerated from 8 h to 4 min, which represents a rate increase of up to 120-fold (Scheme 1).

Scheme 1



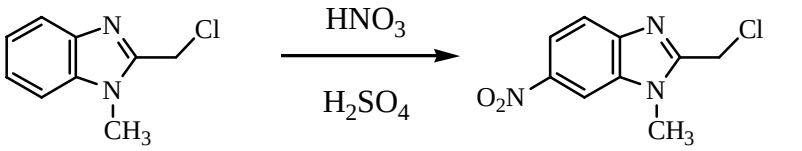
2-Chloromethyl-1*H*-benzimidazole (**1**) can be methylated by using dimethyl sulfate in toluene at 80 °C, during 2 h. These classical operating conditions led us to 2-chloromethyl-1-methyl-1*H*-benzimidazole (**2**) in 49% yield. An attractive alternative to accelerate the methylation reaction was accomplished by applying microwave irradiation.[38] Therefore, the methylation of **1** performed under microwave conditions can be accelerated to 2 min with a higher yield (91%), which represents a 60-fold rate increase (Scheme 2).

Scheme 2



The intermediate compound (**2**) was nitrated using HNO_3-H_2SO_4 mixture, leading to 2-chloromethyl-1-methyl-6-nitro-1*H*-benzimidazole (**3**) in 62% yield (Scheme 3).

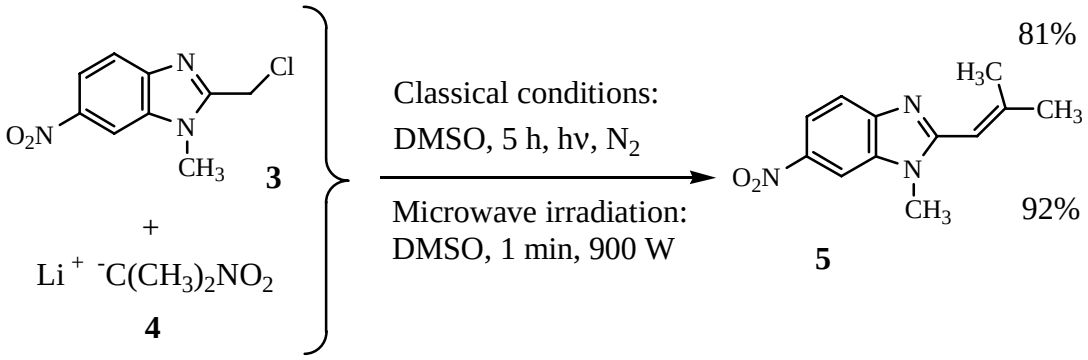
Scheme 3



2 **3** 62%

Derivative (**3**) was treated under nitrogen and photostimulation with 2-nitropropane anion (**4**) during 5 h to give the ethylenic compound (**5**) in 81% yield as shown in Scheme 4. This alkene was classically formed by electron transfer reaction and base-promoted nitrous acid elimination from the *C*-alkylation product. The electron transfer mechanism was confirmed by inhibition studies.[39] Moreover, the importance of the nitro group has been demonstrated by the reaction of **2** with **4** under classical conditions (DMSO, 5 h, hν, N_2) leading to unidentifiable tarry matters.

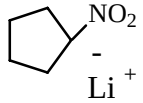
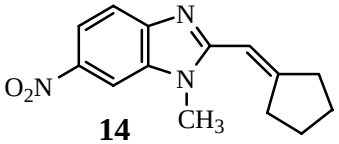
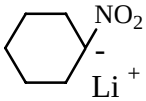
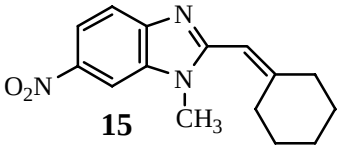
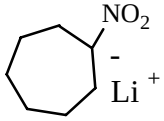
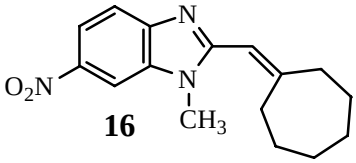
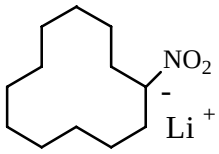
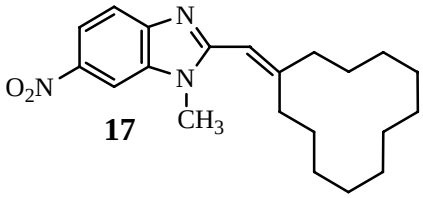
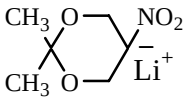
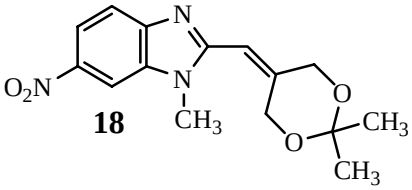
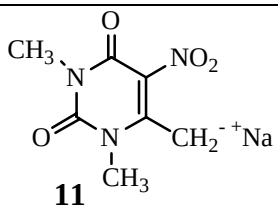
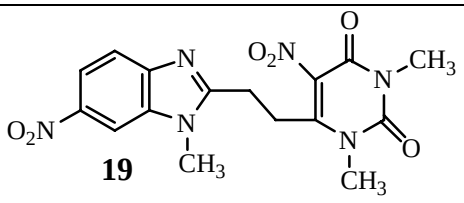
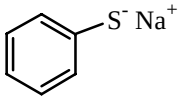
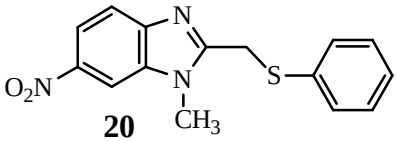
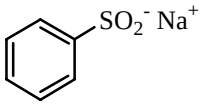
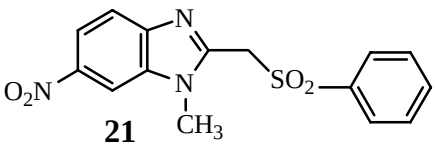
Scheme 4



The same reaction performed during 1 min under microwave irradiation led to 92% yield of **5**. This reaction with 2-nitropropane anion showed that microwave irradiation procedure can induce a fast electron transfer reaction to give in best yield the expected alkene derivative. Therefore, we became interested in preparation of benzimidazole derivatives from different anions according to the microwave irradiation procedure.

The chloride (**3**) reacted with 3 equivalents of different cyclic and heterocyclic nitronate anions (**6-10**) to give the corresponding ethylenic derivatives (**14-18**) as indicated in Table. By using 3 equivalents of the sodium salt of 1,3,6-trimethyl-5-nitro-1*H*-pyrimidine-2,4-dione (**11**), following the same procedure, the reaction with **3** gave the *C*-alkylated product (**19**) in 83% yield. On the other hand, the reaction between *S*-centered anions, the sodium salts of benzenethiol (**12**) and benzenesulfinic acid (**13**) and derivative (**3**) gave the required products (**20**) and (**21**) in respectively 85 and 72% yields. The reactions were fast (1 min), the procedure was simple, and gave the expected products (**14-21**) in good yields (59% to 91%).

Table

Anions	Final products [a]	Yield [b](%)
 **6**	 **14**	64
 **7**	 **15**	71
 **8**	 **16**	74
 **9**	 **17**	59
 **10**	 **18**	91
 **11**	 **19**	83
 **12**	 **20**	85
 **13**	 **21**	72

[a] All reactions were performed by using open Erlenmeyer Pyrex flask. Irradiations were carried out in a domestic microwave oven (Whirlpool MO 111).

[b] Yield of pure isolated products.

In conclusion, we have demonstrated that microwave irradiation can be effectively employed to synthesize new potentially active benzimidazole derivatives in multi-steps: construction of benzimidazole ring, *N*-methylation and electron transfer *C*-alkylation (followed by base-promoted nitrous acid elimination) or *S*-alkylation. These results demonstrate that the versatility of the process as considerable reaction rate enhancement has been observed by bringing down the reaction time from hours to minutes with improved yields as compared to conventional procedure. Study of biological properties of related compounds is under active investigation.

ACKNOWLEDGEMENTS

This work has been supported by the Centre National de la Recherche Scientifique and the Universities of Aix-Marseille. We express our thanks to Professor H. El-Kashef for stimulating discussions and M. Noailly for ^{1}H and ^{13}C NMR spectra recording.

EXPERIMENTAL

Melting points were determined on Büchi B-540 and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3 and of the INP-ENSCT (Toulouse, France). Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker ARX 200 spectrometer. The ^{1}H chemical shifts are reported as ppm downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvent peak: $CDCl_3$ (76.9 ppm). Solvents were dried by conventional methods. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particule size 0.063-0.200 mm, 70-230 mesh ASTM). TLC were performed on 5 cm x 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate solvent. Reactions under microwave irradiation were performed in a domestic microwave oven, Whirlpool MO 111.

2-Chloromethyl-1*H*-benzimidazole (1)

Classical conditions: To a solution of 1,2-phenylenediamine (30 g, 280 mmol) in 5 *N* hydrochloric acid (130 mL), chloroacetic acid (31.8 g, 336 mmol) in solution of 5 *N* hydrochloric acid (110 mL) was added. The reaction mixture was stirred at reflux for 8 h. After basification with 20% ammonia, the residue obtained was washed with water and dried in air. Recrystallization from benzene-hexane (6/4) gave 42.92 g (92%) of yellow solid. **1**, mp 154-155 °C (lit.,[40] 153-155 °C), ^{1}H NMR ($CDCl_3$) δ 4.81 (s, 2H); 7.27-7.36 (m, 2H); 7.56 (m, 2H); 9.14 (br s, 1H).

Microwave irradiation conditions: 1,2-Phenylenediamine (1 g, 9.25 mmol), chloroacetyl chloride (1.13 mL, 13.9 mmol) and 5 g of silica gel (Merck, Geduran SI 60, 70-230 microns, pH = 7, surface area 550 $m^2\ g^{-1}$) was intimately mixed and introduced in a glass vessel (open Erlenmeyer Pyrex flask). The mixture was irradiated in a domestic microwave oven (Whirlpool MO 111) for 4 min at a power of 900 W. After

cooling down, water (20 mL) was added. The reaction mixture was basified with 20% ammonia and the expected product was filtered and recrystallized from benzene-hexane (6/4) giving 1.39 g (90%) of **1**.

2-Chloromethyl-1-methyl-1*H*-benzimidazole (2)

Classical conditions: To a solution of 2-chloromethyl-1*H*-benzimidazole (3 g, 18 mmol) in toluene (10 mL), dimethyl sulfate (2.73 g, 21 mmol), was added dropwise at rt. The reaction mixture was stirred at 80 °C for 2 h. After cooling, water (30 mL) was added and the mixture was basified with 20% ammonia. After filtration, the solution was extracted with chloroform (3 x 50 mL). The organic layer was dried over magnesium sulfate and removed under vacuum. Purification by chromatography on silica gel eluting with chloroform and recrystallization from methanol gave 1.6 g (49%) of yellow solid. **2**, mp 92 °C (lit.,[41] 93-95 °C), ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H); 4.83 (s, 2H); 7.20 (m, 2H); 7.56 (m, 1H); 7.75-7.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 30.11; 36.75; 109.38; 120.11; 122.51; 123.47; 136.06; 141.98; 148.93.

Microwave irradiation conditions: 2-Chloromethyl-1*H*-benzimidazole (0.3 g, 1.8 mmol), dimethyl sulfate (0.45 g, 3.6 mmol) and 1 *N* sodium hydroxide (3 mL) were intimately mixed and introduced in a glass vessel (open Erlenmeyer Pyrex flask). The mixture was irradiated in a domestic microwave oven (Whirlpool MO 111) for 2 min at a power of 500 W. After cooling down, 1 *N* sodium hydroxide (10 mL) was added. The mixture was extracted with chloroform (3 x 10 mL). The solvent was dried over magnesium sulfate and removed under vacuum. Purification by chromatography on silica gel eluting with chloroform and recrystallization from methanol gave 0.30 g (91%) of **2.**

2-Chloromethyl-1-methyl-6-nitro-1*H*-benzimidazole (3)

To a solution of 2-chloromethyl-1-methyl-1*H*-benzimidazole (5 g, 27.7 mmol) in concentrated sulfuric acid (20 mL), fuming nitric acid (3 mL) was added dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 2 h, poured into crushed ice (100 mL), neutralized with sodium carbonate and extracted with dichloromethane (3 x 30 mL). The solvent was dried over magnesium sulfate and removed under vacuum. Purification by chromatography on silica gel eluting with chloroform and recrystallization from ethanol gave 3.87 g (62%) of yellow solid. **3**, mp 190-192 °C, ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H); 4.85 (s, 2H); 7.56 (d, J = 9.0 Hz, 1H); 8.23 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.60 (d, J = 2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 30.84; 36.33; 109.57; 117.01; 119.31; 140.06; 141.28; 143.95; 152.79. Anal. Calcd for $C_9H_8N_3O_2Cl$: C, 47.91; H, 3.57; N, 18.62. Found: C, 48.00; H, 3.53; N, 18.60.

The lithium salt of 2-nitropropane (**4**),[42] nitroalkanes (**6-9**),[43,44] 5,5-dimethyl-2-nitro-[1,3]-dioxane[45,46] (**10**) and the sodium salt of 1,3,6-trimethyl-5-nitro-1*H*-pyrimidine-2,4-dione[47,48] (**11**) were prepared as previously described.

The sodium salts of benzenethiol (**12**) and benzenesulfinic acid (**13**) were commercially available.

Preparation of benzimidazoles (5, 14-21)

Classical conditions: To a solution of 2-nitropropane lithium salt (0.25 g, 2.64 mmol) in dry DMSO (10 mL), was added 2-chloromethyl-1-methyl-6-nitro-1*H*-benzimidazole (0.2 g, 0.88 mmol) under nitrogen and anhydrous conditions. The reaction mixture was irradiated with two 60 W tungsten lamps and stirred at rt during 5 h. Then it was poured into water (100 mL). The aqueous solution was extracted with toluene (3 x 20 mL). The organic extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from ethanol gave 0.165 g (81%) of **5**.

Microwave irradiation conditions: The appropriate salt of nitro or sulfur derivatives (**4, 6-13**) (2.64 mmol), 2-chloromethyl-1-methyl-6-nitro-1*H*-benzimidazole (0.88 mmol) and silica gel (Merck, Geduran SI 60, 70-230 microns, pH = 7, surface area 550 $m^2 g^{-1}$, 1 g) in DMSO (4 mL) were intimately mixed and placed in an open Erlenmeyer Pyrex flask. The reaction mixture was irradiated in a domestic microwave oven (Whirlpool MO 111) for 1 min at a power of 900 W. After cooling, methanol (10 mL) was added. After filtration over anhydrous magnesium sulfate, the reaction mixture was evaporated. The crude product was dissolved in water (100 mL). After extraction with toluene (3 x 20 mL), the organic extracts were then dried over anhydrous magnesium sulfate, evaporated under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from ethanol gave the expected products (**5, 14-21**).

1-Methyl-2-(2-methylpropenyl)-6-nitro-1*H*-benzimidazole (5)

Yellow solid, 92% yield, mp 145-146 °C, ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H); 2.26 (s, 3H); 3.75 (s, 3H); 6.17 (s, 1H); 7.30 (d, J = 9.0 Hz, 1H); 8.14 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.77 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 20.97; 27.67; 30.27; 105.87; 110.53; 118.06; 118.96; 134.42; 142.35; 147.51; 151.15; 157.26. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.03; H, 5.61; N, 18.08.

2-Cyclopentylidenemethyl-1-methyl-6-nitro-1*H*-benzimidazole (14)

Yellow solid, 64% yield, mp 147-149 °C, ^{1}H NMR ($CDCl_3$) δ 1.76-1.87 (m, 4H); 2.62 (t, J = 6.2 Hz, 2H); 3.00 (t, J = 6.2 Hz, 2H); 3.80 (s, 3H); 6.43 (s, 1H); 7.76 (d, J = 9.0 Hz, 1H); 8.14 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.24 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 25.81; 27.53; 30.52; 30.73; 38.25; 108.13; 118.38; 118.89. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.28; H, 5.83; N, 16.31.

2-Cyclohexylidenemethyl-1-methyl-6-nitro-1*H*-benzimidazole (15)

Yellow solid, 71% yield, mp 168-169 °C, ^{1}H NMR ($CDCl_3$) δ 1.58-1.68 (m, 6H); 2.40 (t, J = 6.0 Hz, 2H); 2.94 (t, J = 6.0 Hz, 2H); 3.82 (s, 3H); 6.18 (s, 1H); 7.75 (d, J = 9.0 Hz, 1H); 8.18 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.26 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 26.20; 27.75; 28.68; 30.30; 30.67; 38.32; 107.56; 118.08; 118.94. Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.34; H, 6.27; N, 15.47.

2-Cycloheptylidenemethyl-1-methyl-6-nitro-1*H*-benzimidazole (16)

Yellow solid, 74% yield, mp 127-128 °C, ^{1}H NMR ($CDCl_3$) δ 1.58-1.61 (m, 6H); 1.74 (m, 2H); 2.57 (t, J = 5.8 Hz, 2H); 3.06 (t, J = 5.8 Hz, 2H); 3.81 (s, 3H); 6.24 (s, 1H); 7.77 (d, J = 9.0 Hz, 1H); 8.12 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.24 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 26.43; 28.74; 29.68; 29.80; 30.25; 33.07; 39.60; 105.76; 109.74; 117.94; 118.88; 134.27; 142.79; 147.87; 156.04; 161.43. Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.41; H, 6.75; N, 14.75.

2-Cyclododecylidenemethyl-1-methyl-6-nitro-1*H*-benzimidazole (17)

Yellow solid, 59% yield, mp 162-163 °C, ^{1}H NMR ($CDCl_3$) δ 1.25-1.38 (m, 14H); 1.61-1.77 (m, 4H); 2.26 (t, J = 6.3 Hz, 2H); 2.45 (t, J = 6.3 Hz, 2H); 3.80 (s, 3H); 6.28 (s, 1H); 7.74 (d, J = 9.0 Hz, 1H); 8.16 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.24 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 25.87; 25.91; 26.09; 26.27; 26.40; 27.35; 28.71; 29.69; 29.85; 30.20; 33.17; 39.68; 105.71; 108.64; 115.98; 119.72; 134.46; 143.29; 147.75; 156.15; 161.49. Anal. Calcd for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 70.85; H, 8.12; N, 11.80.

2-(2,2-Dimethyl-[1,3]-dioxan-5-ylidenemethyl)-1-methyl-6-nitro-1*H*-benzimidazole (18)

Yellow solid, 91% yield, mp 165-167 °C, ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 6H); 3.80 (s, 3H); 4.45 (s, 2H); 5.06 (s, 2H); 6.21 (s, 1H); 7.33 (d, J = 9.0 Hz, 1H); 8.17 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.57 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 23.95; 30.30; 62.24; 63.79; 99.95; 106.19; 108.95; 115.94; 118.40; 139.11; 151.19; 152.63. Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.33; H, 5.61; N, 13.82.

1,3-Dimethyl-6-[2-(1-methyl-6-nitro-1*H*-benzimidazol-2-yl)ethyl]-5-nitro-1*H*-pyrimidine-2,4-dione (19)

Yellow solid, 83% yield, mp 297-299 °C, ^{1}H NMR ($CDCl_3$) δ 3.33-3.36 (m, 2H); 3.41 (s, 3H); 3.59-3.61 (m, 2H); 3.69 (s, 3H); 3.84 (s, 3H); 7.49 (d, J = 9.0 Hz, 1H); 8.25 (dd, J = 9.0 Hz and 2.0 Hz , 1H); 8.61 (d, J = 2.0 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 25.69; 27.16; 29.75; 31.37; 33.71; 111.79; 115.82; 118.90; 130.20; 141.74; 142.28; 143.77; 151.43; 153.72; 156.28; 158.51. Anal. Calcd for $C_{16}H_{16}N_6O_6$: C, 49.49; H, 4.15; N, 21.64. Found: C, 49.39; H, 4.09; N, 21.60.

1-Methyl-6-nitro-2-phenylsulfanylmethyl-1*H*-benzimidazole (20)

Yellow solid, 85% yield, mp 142-144 °C, ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H) ; 5.64 (s, 2H); 7.43-7.54 (m, 5H); 7.60 (d, J = 9.0 Hz, 1H); 8.07 (dd, J = 9.0 Hz and 2.2 Hz, 1H); 8.25 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 30.82; 58.50; 109.61; 116.93; 128.58; 128.73; 129.84; 133.73; 141.53; 143.79; 152.49; 165.72. Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.05; H, 4.33; N, 14.02.

2-Benzenesulfonylmethyl-1-methyl-6-nitro-1*H*-benzimidazole (21)

Yellow solid, 72% yield, mp 255-256 °C (lit.,[49] 255.5-256.5 °C), ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H); 4.70 (s, 2H); 7.36-7.58 (m, 2H); 7.60-7.66 (m, 3H); 8.14 (d, J = 9.0 Hz, 1H); 8.21 (dd, J = 9.0 Hz and 2.2 Hz,

1H); 8.45 (d, J = 2.2 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 31.52; 55.43; 106.91; 109.92; 116.79; 118.42; 119.28; 120.24; 128.45; 129.40; 134.74; 137.36. Anal. Calcd for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68. Found: C, 54.37; H, 3.99; N, 12.70.

REFERENCES

1. R. A. Abramovitch, *Org. Prep. Proced. Int.*, 1991, **23**, 685.
2. S. Caddick, *Tetrahedron*, 1995, **51**, 10403.
3. C. Gabriel, S. Gabriel, E. H. Grant, B. S. J. Halstead, and D. M. P. Mingos, *Chem. Soc. Rev.*, 1998, **27**, 213.
4. S. Deshayes, M. Liagre, A. Loupy, J.-L. Luche, and A. Petit, *Tetrahedron*, 1999, **55**, 10851.
5. L. Perreux and A. Loupy, *Tetrahedron*, 2001, **57**, 9199.
6. P. Lidström, J. Tierney, B. Wathey, and J. Westman, *Tetrahedron*, 2001, **57**, 9225.
7. G. W. Kabalka, P. P. Wadgaonkar, and N. Chatla, *Synth. Commun.*, 1990, **20**, 293.
8. G. W. Kabalka and R. M. Pagni, *Tetrahedron*, 1997, **53**, 7999.
9. M. Puciova, P. Ertl, and S. Toma, *Collect. Czech. Chem. Commun.*, 1994, **59**, 175.
10. T. Besson, M.-J. Dozias, J. Guillard, P. Jacquault, M.-D. Legoy, and C. W. Rees, *Tetrahedron*, 1998, **54**, 6475.
11. G. Sabitha, R. S. Babu, and J. S. Yadav, *Synth. Commun.*, 1998, **28**, 4571.
12. C. T. Brain and J. M. Paul, *Synlett*, 1999, 1642.
13. R. S. Varma and D. Kumar, *Tetrahedron Lett.*, 1999, **40**, 7665.
14. M. Kidwai, K. R. Bhushan, P. Sapra, R. K. Saxena, and R. Gupta, *Bioorg. Med. Chem.*, 2000, **8**, 69.
15. A. Ben-Alloum, S. Bakkas, and M. Soufiaoui, *Tetrahedron Lett.*, 1998, **39**, 4481.
16. R. S. Varma and R. Dahiya, *Tetrahedron*, 1998, **54**, 6293.
17. T. N. Danks, *Tetrahedron Lett.*, 1999, **40**, 3957.
18. K. Bougrin, A. Loupy, A. Petit, B. Daou, and M. Soufiaoui, *Tetrahedron*, 2001, **57**, 163.
19. W. Nawrocka, *Boll. Chim. Farm.*, 1996, **135**, 18.
20. P. Winstanley, *Lancet*, 1998, **352**, 1080.
21. A. Carpio, *J. Neurol., Neurosurg. Psychiatry*, 1999, **66**, 411.
22. H. Al-Muhaimeed, *J. Int. Med. Res.*, 1997, **25**, 175.
23. J. E. Richter, *Am. J. Gastroenterol.*, 1997, **92**, 34.
24. J. B. Cheng, K. Cooper, A. J. Duplantier, J. F. Eggler, K. G. Kraus, S. C. Marshall, A. Marfat, H. Masamune, J. T. Shirley, J. E. Tickner, and J. P. Umland, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1969.
25. A. P. Thomas, C. P. Allott, K. H. Gibson, J. S. Major, B. B. Masek, A. A. Oldham, A. H. Ratcliffe, D. A. Roberts, S. T. Russell, and D. A. Thomason, *J. Med. Chem.*, 1992, **35**, 877.

26. K. Kubo, Y. Inada, Y. Kohara, Y. Sugiura, M. Ojima, K. Itoh, Y. Furukawa, K. Nishikawa, and T. Naka, *J. Med. Chem.*, 1993, **36**, 1772.
27. M. B. Arnold, T. C. Britton, R. F. Bruns, B. E. Cantrell, A. M. Happ, P. A. Hipskind, J. J. Howbert, K. L. Lobb, J. A. Nixon, P. L. Ornstein, E. C. Smith, H. Zarrinmayeh, and D. M. Zimmerman, *Int. Pat. Appl.*, 1997, WO 9725041 (*Chem. Abstr.*, 1997, **127**, 668) [CAN 127:161824].
28. P. Vanelle and M. P. Crozet, *Recent Res. Devel. Organic Chem.*, 1998, **2**, 547.
29. P. Vanelle, K. Benakli, L. Giraud, and M. P. Crozet, *Synlett*, 1999, 801.
30. P. Vanelle, T. Terme, and M. P. Crozet, *Tetrahedron Lett.*, 2000, **41**, 6383.
31. M. D. Crozet, A. Gellis, M. Kaafarani, M. P. Crozet, and P. Vanelle, *Heterocycles*, 2001, **55**, 1271.
32. P. Vanelle, A. Gellis, M. Kaafarani, J. Maldonado, and M. P. Crozet, *Tetrahedron Lett.*, 1999, **40**, 4343.
33. A. Gellis, S. Djekou, J. Maldonado, M. P. Crozet, and P. Vanelle, *Actual. Chim. Ther.*, 2000, **26**, 259.
34. A. Gellis, Y. Njoya, M. P. Crozet, and P. Vanelle, *Synth. Commun.*, 2001, **31**, 1257.
35. J. G. Smith and I. Ho, *Tetrahedron Lett.*, 1971, 3541.
36. M. A. Phillips, *J. Chem. Soc.*, 1928, 172.
37. L. K. Thompson, B. S. Ramaswamy, and E. A. Seymour, *Can. J. Chem.*, 1977, **55**, 878.
38. W.-C. Shieh, S. Dell, and O. Repic, *Org. Lett.*, 2001, **3**, 4279.
39. M. Chanon and M. L. Tobbe, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 1.
40. M. Raban, H. Chang, L. Craine, and E. Hortelano, *J. Org. Chem.*, 1985, **50**, 2205.
41. S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, 1966, **14**, 1219.
42. R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Am. Chem. Soc.*, 1965, **87**, 4520.
43. K. E. Gilbert and W. T. Borden, *J. Org. Chem.*, 1979, **44**, 659.
44. P. Vanelle, N. Madadi, C. Roubaud, J. Maldonado, and M. P. Crozet, *Tetrahedron*, 1991, **47**, 5173.
45. G. B. Linden and M. H. Gold, *J. Org. Chem.*, 1956, **21**, 1175
46. H. Piotrowska, T. Urbanski, and I. Kmiotek, *Roczn. Chem.*, 1973, **47**, 409.
47. W. Pfleiderer and H. Mosthaf, *Chem. Ber.*, 1957, **90**, 728.
48. M. P. Crozet, A. Gellis, C. Pasquier, P. Vanelle, and J.-P. Aune, *Tetrahedron Lett.*, 1995, **36**, 525.
49. M. K. Bernard, *Pol. J. Chem.*, 1995, **69**, 1120.