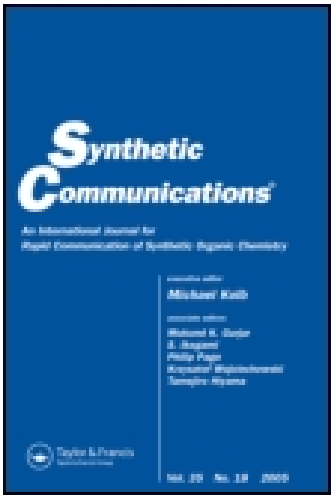


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

General Synthesis of 1-Substituted 2-Methylbenzimidazoles from Ketones and 2-Aminoacetanilide

Svetlana A. Burova [a], Roman Davis [a], Russ N. Fitzgerald [a], Byron S. Johnson [a] & Richard T. Matsuoka [a]
[a] Chemical Development, GlaxoSmithKline, Research Triangle Park, North Carolina

Published online: 10 Sep 2007.

To cite this article: Svetlana A. Burova, Roman Davis, Russ N. Fitzgerald, Byron S. Johnson & Richard T. Matsuoka (2007) General Synthesis of 1-Substituted 2-Methylbenzimidazoles from Ketones and 2-Aminoacetanilide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:18, 3029-3039, DOI: 10.1080/00397910701542996

To link to this article: http://dx.doi.org/10.1080/00397910701542996

Synthetic Communications®, 37: 3029–3039, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701542996

General Synthesis of 1-Substituted 2-Methylbenzimidazoles from Ketones and 2-Aminoacetanilide

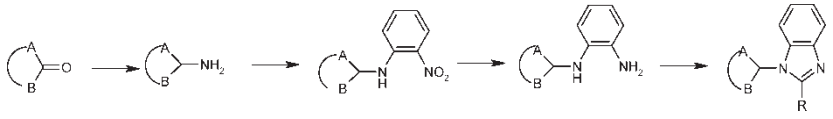
Svetlana A. Burova, Roman Davis, Russ N. Fitzgerald, Byron S. Johnson, and Richard T. Matsuoka
Chemical Development, GlaxoSmithKline, Research Triangle Park, North Carolina

Abstract: A novel method for preparation of 1-substituted benzimidazoles via reductive amination of ketones with N-differentiated 1,2-diaminobenzenes is described. The method appears to be general in application to acyclic and cyclic ketones, as well as heteroatom-substituted cyclic ketones.

Keywords: benzimidazoles, reductive amination, cyclization

In the course of developing a drug candidate, we required a short and efficient route to benzimidazoles substituted at the 1-position with branched or cyclic substituents. These pharmaceutically useful moieties[1] are typically synthesized from ketones via the multistep sequence of reductive amination,[2] reaction of the resulting amine with 2-halonitrobenzenes, nitro reduction, and cyclization with orthoesters (Scheme 1). This multistep synthesis is tedious and requires handling of often unstable 1,2-diaminobenzenes. Other synthetic methods are specific for 1-n-alkylbenzimidazoles[3] or N-unsubstituted benzimidazoles.[4]

Received in the USA January 31, 2007
Address correspondence to Roman Davis, Chemical Development, GlaxoSmithKline, 5 Moore Drive,Research Triangle Park, NC 27709. E-mail: roman.d.davis@gsk.com

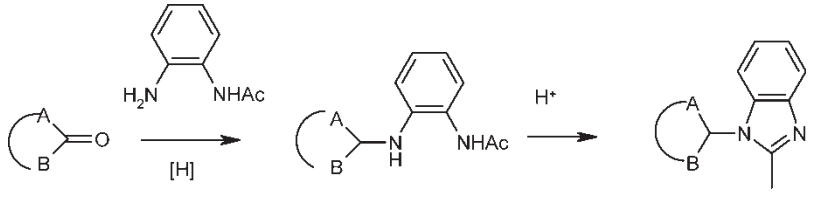


Scheme 1.

Our initial efforts proved ineffective. These included alkylation of benzimidazoles with cycloalkyl sulfonates, reductive amination of diaminobenzenes giving complex mixtures, and Ti-mediated amination designed for anilines.[5]

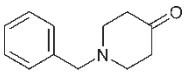
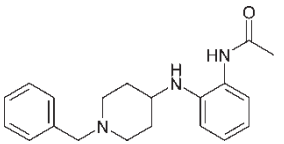
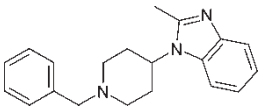
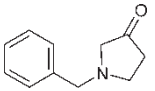
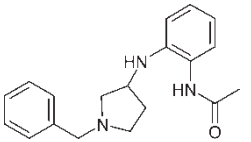
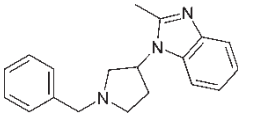
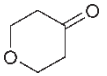
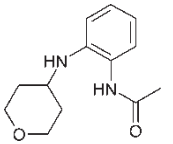
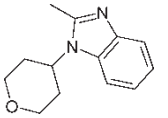
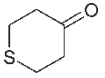
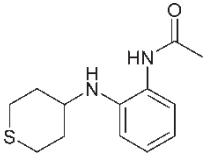
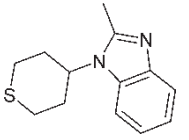
We therefore turned our attention to reductive amination of ketones with N-differentiated 1,2-diaminobenzenes. We report herein an efficient two-step synthesis of 1-substituted 2-methylbenzimidazoles, which can be applied to cyclic or acyclic ketones. The synthesis entails reductive amination with 2-aminoacetanilide, followed by acid-mediated cyclization (Scheme 2). We have found no other examples of N-differentiated diaminobenzenes participating in reductive amination and therefore consider this to be a novel approach.

The reductive amination requires at least 6 equivalents of acetic acid (HOAc) and 1.5 equivalents of sodium triacetoxyborohydride (STAB), in dichloromethane (DCM) or dichloroethane (DCE) solvent. Additional HOAc does not affect the reaction adversely, but less HOAc significantly retards the reaction. Trifluoroacetic acid (TFA) replacement for all or part of HOAc shortens the reaction time. Severe safety and exposure considerations are associated with TFA. Material Safety Data information includes: Danger! Corrosive. Causes Burns. Harmful if swallowed, inhaled, or absorbed through Skin. Material is extremely destructive to the upper respiratory tract, eyes, and skin. Other strong acids, such as methanesulfonic acid, proved inferior, leading to decomposition of the product anilide. During the course of manuscript submission, the use of excess HOAc or replacing HOAc with TFA was reported for reductive amination of 2-chloro-3-aminopyridines.[6] Other solvents were not as effective, in contrast to literature precedences[7] that indicated that other solvents produce only kinetic effects. Many of the resulting alkylated anilides were not fully soluble in DCM.



Scheme 2.

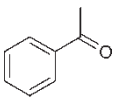
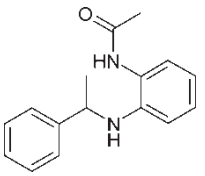
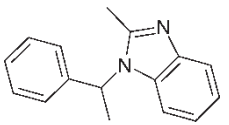
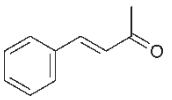
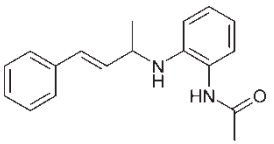
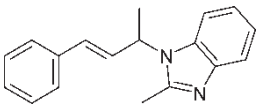
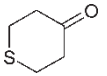
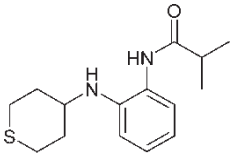
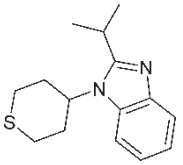
Table 1. Reductive amination of ketones with 2-aminoanilides and conversion to benzimidazoles

Entry	Substrate ketone a	Anilide b	Yield (%)	Benzimidazole c	Yield (%)
1			77		84
2			86		68
3			79		67
4			83		67

(*continued*)

Table 1. Continued

Entry	Substrate ketone a	Anilide b	Yield (%)	Benzimidazole c	Yield (%)
5			62 (over 2 crops)		Not isolated[a]
6			0[b]		Not processed
7			90		30

8			66		67[c]
9			63		57[d]
10			55		13%; not isolated

[a]Cyclization gave a complex mixture, and the desired benzimidazole was not isolated.
[b]Only reduction to alcohol was observed.
[c]De-acylated diamine, 25%, was also isolated.
[d]Mixture of 90:10 trans–cis isomers.

Therefore, 2-methyltetrahydrofuran (MTHF) was used as a cosolvent for base-extractive workup. MTHF has solubility properties similar to tetrahydrofuran (THF) but easily separates from water. It is readily available, inexpensive, and environmentally benign.[8] The product anilides were crystallized through partial concentration of the DCM–MTHF mixture to remove the DCM and addition of an alkane such as heptane or isooctane.

Although each reaction described was optimized for the substrate required by our development program, the method is general for many substrates (see Table 1).

The reductive amination reactions were especially efficient for cyclic ketones containing heteroatoms in the ring (entries 1–4). The reaction with β-tetrolone (entry 7) gave 90% yield, whereas α-tetrolone (entry 6) gave only the ketone reduction product. However, its open analog, acetophenone (entry 8), gave 68% yield. From these results, we infer that conformational restrictions in α-tetralone inhibit imine or enamine formation, thus leading only to ketone reduction. Conversely, enamine formation in β-tetralone would be assisted by enolization and conjugation, where reduction may also take place at the enamine. 4-*tert*-Butylcyclohexanone (entry 5) gave a 4:1 mixture of two isomers, from which the major isomer could be crystallized in 62% yield over two crops. This substrate was not further investigated. However, the isomer selectivity, applied to bicyclic ketones, such as tropanone derivatives, and hydroxylated cyclic ketones, will be the subject of a subsequent manuscript highlighting ReactIR data from the reductive amination.

The reactions were not affected by unsaturation elsewhere in the molecule (entry 9). However, 2-cyclohexenone gave a complex mixture of isomers. Other 2-aminoanilides (entry 10) also underwent reductive amination. Cyclization to the benzimidazoles was easily achieved with 12 M aqueous hydrogen chloride in ethanol. Low cyclization yields for some substrates reflect difficulty of crystallization rather than reaction performance, so this step will require optimization for each desired substrate. Surprisingly, the isobutyrylanilide (entry 10) gave predominately de-acylation and only 13% (by HPLC) of the cyclized product.

In summary, we have developed an efficient two-step synthesis of 1-substituted 2-methylbenzimidazoles, which can be applied to cyclic or acyclic ketones. The method operates across a range of ketones and is especially robust in cyclic ketones containing heteroatoms in the ring.

EXPERIMENTAL

Starting materials, reagents, and solvents were purchased from bulk commercial sources and were used without further purification. All temperatures are uncorrected. HPLC reaction monitoring and analysis was conducted on a Luna $C_{18}(2)$ 50 mm × 2 mm, 3-μm column, at 40°C, flow rate of 1 mL/min, and UV visualization at 220 nm; mobile phase A: H_2O (0.05%), mobile

phase B: CH_3CN (0.05%); gradient: 0–95% B over 8 min. ^1H NMR spectra were measured at 400 MHz, and ^{13}C NMR spectra were measured at 100 MHz.

High-resolution mass spectral (HRMS) data were obtained using a Waters Micromass Q-Tof 2 with electrospray ionization (ESI). HRMS data for each compound were accurate within 5 ppm.

Reductive Amination

To a mixture of 2-aminoacetanilide (7 g, 46.6 mmol), ketone (51.3 mmol, 1.1 eq.), and $NaBH(OAc)_3$ (14.8 g, 70 mmol. 1.5 eq.) in CH_2Cl_2 (56 mL) at 0–5°C, was added AcOH (10.6 mL, 6.0 eq.), maintaining the internal temperature at $\leq$ 20°C. The solution was stirred at approximately 20°C for 4 h or until complete by HPLC. MTHF (140 mL), was added to the mixture and the pH was adjusted to 13 with 10 N NaOH (50 mL). Where required, the biphasic mixture was heated to maintain a solution. The organic layer was washed with H_2O (70 mL) and reduced under vacuum by approximately 60%. Heptane was added as an antisolvent, and the resulting solid was isolated via filtration and dried under vacuum at approximately 50°C. Where required, the compound was recrystallized or purified chromatographically to provide an analytically pure sample. Yields: 55–90%.

Data

N-(2-{[1-(Phenylmethyl)-4-piperidinyl]amino}phenyl)acetamide **(1b)**: ^1H NMR (DMSO-d_6): δ 9.09 (s, 1H), 7.28–7.33 (m, 4H), 7.22–7.25 (m, 1H), 7.12 (d, $J = 7.6$ Hz, 1H), 6.97 (t, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 6.53 (t, $J = 7.6$ Hz, 1H), 4.59 (d, $J = 7.6$ Hz, 1H), 3.46 (s, 2H), 3.22–3.29 (m, 1H), 2.76 (d, $J = 11.6$ Hz, 2H), 2.08 (t, $J = 11.2$ Hz, 2H), 2.03 (s, 3H), 1.9 (d, $J = 11.2$ Hz, 2H), 1.41 (q, $J = 11.6$ Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ168.5, 141.2, 138.7, 128.7, 128.1, 126.8, 126.1, 126.0, 123.8, 115.5, 111.6, 62.2, 51.9, 49.1, 31.8, 23.4. Mp: 159.0–160.3°C. HRMS: calc. for $C_{20}H_{26}N_3O$: 324.2076. Found 324.2076.

N-(2-{[1-(Phenylmethyl)-3-pyrrolidinyl]amino}phenyl)acetamide **(2b)**: ^1H NMR (DMSO-d_6): δ 9.13 (s, 1H), 7.30–7.31 (m, 4H), 7.21–7.24 (m, 1H), 7.15 (d, $J = 7.6$ Hz, 1H), 6.97 (t, $J = 7.6$ Hz, 1H), 6.54–6.57 (m, 2H), 4.92 (d, 6.4 Hz, 1H), 3.82–3.93 (m, 1H), 3.53 (q, $J = 12.8$ Hz, 2H), 2.78 (t, $J = 8.0$ Hz, 1H), 2.63 (q, $J = 8.4$ Hz, 1H), 2.45 (q, $J = 8.0$ Hz, 1H), 2.37 (dd, $J = 9.2$, 4.4 Hz, 1H), 2.21–2.27 (m, 1H), 1.55–1.63 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 168.5, 141.5, 139.0, 128.5, 128.2, 126.8, 126.0, 125.6, 124.1, 115.9, 111.8, 60.2, 59.5, 52.6, 51.7, 32.0, 23.4. Mp: 127.3–128.3°C.

Anal. calc. for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58. Found: C, 73.47; H, 7.51; N, 13.58. HRMS: calc. for $C_{19}H_{24}N_3O$: 310.1919. Found 310.1916.

N-[2-(Tetrahydro-2*H*-pyran-4-ylamino)phenyl]acetamide **(3b)**: ^{1}H NMR (DMSO-d_6): δ 9.08 (s, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 6.98 (t, $J = 8.0$ Hz, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 6.55 (t, $J = 8.0$ Hz, 1H), 4.65 (d, $J = 8.8$ Hz, 1H), 3.83–3.88 (m, 2H), 3.39–3.51 (m, 3H), 3.42 (t, $J = 11.2$ Hz, 2H), 2.04 (s, 3H), 1.88 (d, $J = 11.2$ Hz, 2H), 1.39 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 168.5, 140.9, 126.1, 126.0, 123.9, 115.7, 111.7, 65.9, 48.0, 32.8, 23.4. Mp: 183.2–185.0°C. Anal. calc. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.89; H, 7.76; N, 11.91. HRMS: calc. for $C_{13}H_{19}N_2O_2$: 235.1447. Found 235.1454.

N-[2-(Tetrahydro-2*H*-thiopyran-4-ylamino)phenyl]acetamide **(4b)**: ^{1}H NMR (DMSO-d_6): δ 9.08 (s, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.98 (t, $J = 8.0$ Hz, 1H), 6.66 (d, $J = 8.0$ Hz, 1H), 6.55 (t, $J = 8.0$ Hz, 1H), 4.67 (d, $J = 7.6$ Hz, 1H), 3.29–3.36 (m, 1H), 2.63–2.75 (m, 4H), 2.16–2.19 (m, 2H), 2.04 (s, 3H), 1.47–1.57 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 168.5, 140.7, 126.1, 126.1, 123.8, 115.6, 111.5, 49.6, 33.7, 26.8, 23.4. Mp: 145.0–146.0°C. Anal. calc. for $C_{13}H_{18}N_2OS$: C, 62.37; H, 7.25; N, 11.19. Found; C, 62.31; H, 7.27; N, 11.14. HRMS: calc. for $C_{13}H_{19}N_2O_S$: 251.1218. Found 251.1212.

N-(2-{[4-(1,1-Dimethylethyl)cyclohexyl]amino}phenyl)acetamide **(5b)**: ^{1}H NMR (DMSO-d_6): δ 9.40 (s, 1H), 7.00 (t, $J = 8.0$ Hz, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 6.64 (d, $J = 8$ Hz, 1H), 6.54 (t, $J = 7.6$ Hz, 1H), 4.55 (d, $J = 8.0$ Hz, 1H), 3.6–3.67 (m, 1H), 2.01 (s, 3H), 1.82 (d, $J = 11.6$ Hz, 2H), 1.41–1.48 (m, 4H), 1.13–1.23 (m, 2H), 0.96–1.02 (m, 1H), 0.82 (s, 9H). ^{13}C NMR (DMSO-d_6): δ 168.7, 142.0, 126.8, 126.5, 124.3, 115.7, 112.4, 47.3, 45.7, 32.5, 29.7, 27.5, 23.1, 21.0. Mp: 140–141°C. Anal. calc. for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71. Found; C, 74.66; H, 9.88; N, 9.46. HRMS: calc. for $C_{18}H_{29}N_2O$: 289.2280. Found 289.2273.

N-[2-(1,2,3,4-Tetrahydro-2-naphthalenylamino)phenyl]acetamide **(7b)**: ^{1}H NMR (CD_2Cl_2): 7.27 (d, $J = 7.6$ Hz, 1H), 7.13–7.06 (m, 5H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.75 (dd, $J = 7.6$, 7.6 Hz, 1H), 3.93 (1H, brs), 3.74 (m, 1H), 3.16 (dd, $J = 8.0$, 4.0 Hz, 1H), 2.92 (m, 2H), 2.70 (dd, $J = 8.8$, 8.2, Hz, 1H), 2.18 (m, 1H), 2.09 (s, 3H0, 1.75 (m, 1H). ^{13}C NMR (CD_2Cl_2): 169.5, 142.0, 136.6, 135.4, 129.9, 129.8, 129.2, 127.7, 126.5, 126.4, 126.2, 49.6, 36.8, 29.8, 28.2, 24.1. HRMS: calc. for $C_{18}H_{21}N_2O$: 281.1654. Found 281.1655.

N-{2-[(1-Phenylethyl)amino]phenyl}acetamide **(8b)**: ^{1}H NMR (CD_2Cl_2): 7.37 (m, 2H), 7.31 (m, 2H), 7.22 (m, 1H), 7.14 (m, 1H), 6.95 (m, 1H), 6.64 (m, 1H), 6.47 (m, 1H), 4.57–4.47 (m, 3H), 2.18 (s, 3H), 1.5 (d, 3H, $J = 8.0$ Hz). ^{13}C NMR (CD_2Cl_2): 169.85, 145.8, 142.5, 129.1, 127.7, 127.4, 126.4, 117.8, 114.4, 53.9, 25.6, 24.1. HRMS: calc. for $C_{16}H_{19}N_2O$: 255.1497. Found 255.1494.

N-(2-{[(2*E*)-1-Methyl-3-phenyl-2-propen-1-yl]amino}phenyl)acetamide **(9b)**: ^{1}H NMR (CD_2Cl_2): 7.36 (m, 2H), 7.30 (m, 2H), 7.22 (m, 2H), 7.09 (m, 1H), 6.80 (d, 1H, $J = 10$ Hz), 6.71 (m, 1H), 6.58 (d, 1H, $J = 20.0$ Hz), 6.22 (dd, 1H, $J = 20.0$, 7.5 Hz), 4.13 (m, 1H0, 2.16 (s, 3H), 1.4 (d, 3H, $J = 8.0$ Hz). ^{13}C NMR (CD_2Cl_2): 169.9, 142.5, 137.5, 133.6, 129.8, 129.0, 127.8, 127.7, 126.8, 126.5, 118.1, 51.5, 24.1, 22.4. HRMS: calc. for $C_{18}H_{21}N_2O$: 281.1654. Found 281.1649.

2-Methyl-*N*-[2-(tetrahydro-2*H*-thiopyran-4-ylamino)phenyl]propanamide **(10b)**: ^{1}H NMR (DMSO-d_6): δ 9.08 (s, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.99 (t, $J = 8.0$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 6.56 (t, $J = 8.0$ Hz, 1H), 4.51 (d, $J = 8.0$ Hz, 1H), 3.32–3.38 (m, 1H), 2.60–2.73 (m, 5H), 2.14–2.18 (m, 2H), 1.46–1.56 (m, 2H), 1.10 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (DMSO-d_6): δ 175.5, 140.8, 126.2, 123.9, 115.9, 111.8, 49.4, 34.3, 33.7, 26.5, 19.7. Mp: 165.4-166.4°C. Anal. calc. for $C_{15}H_{22}N_2OS$: C, 64.71; H, 7.96; N, 10.06. Found: C, 64.51; H, 8.04; N, 9.98. HRMS: Calc. for $C_{15}H_{23}N_2OS$: 279.1531. Found 279.1538.

Cyclization to Benzimidazoles

To a mixture of the acetamide (43 mmol) in EtOH (80 mL), 12 M HCl (11 mL, 129 mmol, 3 eq.) was added. The solution was heated to approximately 70°C and stirred for 4 h or until the reaction was complete by HPLC. The solution was cooled to approximately 20°C. Some products crystallized, and these were isolated directly from the mixture as HCl salts. However, to eliminate potential mixtures of mono and di HCl salts, the preferred form of the isolated product was the freebase. The freebase product was obtained by neutralization of the reaction with NaOH and extraction into CH_2Cl_2. The product was isolated either by crystallization with heptane or concentrating to dryness. The solid was isolated via filtration and dried under vacuum at approximately 50°C. Where required, the compound was recrystallized or purified chromatographically. Yields: 57–84%.

Data

2-Methyl-1-[1-(phenylmethyl)-4-piperidinyl]-1*H*-benzimidazole **(1c)**: ^{1}H NMR (DMSO-d_6): δ 7.58 (d, $J = 7.6$ Hz, 1H), 7.50 (d, $J = 7.6$ Hz, 1H), 7.32–7.28 (m, 4H), 7.24–7.28 (m, 1H), 7.08–7.16 (m, 2H), 4.24–4.32 (m, 1H), 3.56 (s, 2H), 2.96 (d, $J = 12.0$ Hz, 2H), 2.55 (s, 3H), 2.36 (qd, $J = 12$, 4 Hz, 2H), 2.17 (t, $J = 12$ Hz, 2H), 1.80 (d, $J = 12$ Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 151.4, 142.9, 138.3, 133.6, 128.8, 128.2, 126.9, 121.2, 120.8, 118.6, 111.5, 61.9, 53.7, 52.4, 29.8, 14.5. HRMS: calc. for $C_{20}H_{24}N_3$: 306.1970. Found 306.1984.

2-Methyl-1-[1-(phenylmethyl)-3-pyrrolidinyl]-1*H*-benzimidazole **(2c)**: ^{1}H NMR (DMSO-d_6): δ 7.98 (d, $J = 7.6$ Hz, 1H), 7.48 (d, $J = 7.6$ Hz, 1H),

7.38 (d, $J = 7.2$ Hz, 2H), 7.32 (t, $J = 7.6$ Hz, 2H), 7.23 (t, $J = 7.2$ Hz, 1H), 7.09–7.16 (m, 2H), 5.09–5.16 (m, 1H), 3.78 (d, $J = 12.0$ Hz, 1H), 3.60 (d, $J = 12.0$ Hz, 1H), 3.11 (t, $J = 8.4$ Hz, 1H), 2.96 (dd, $J = 10.4$, 3.6 Hz, 1H), 2.70 (t, $J = 10.0$ Hz, 1H), 2.54 (s, 3H), 2.33–2.45 (m, 2H), 2.01–2.11 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 151.7, 142.9, 138.8, 132.7, 128.5, 128.2, 127.0, 121.1, 121.1, 118.4, 111.8, 59.2, 57.2, 53.6, 53.4, 30.3, 14.1. Mp: 93.8–94.5°C. Anal. calc. for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.02; H, 7.46; N, 14.55. HRMS: Calc. for $C_{19}H_{22}N_3$: 292.1814. Found 292.1821.

2-Methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-benzimidazole **(3c)**: ^{1}H NMR (DMSO-d_6): δ 7.71 (d, $J = 8.8$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.09–7.15 (m, 2H), 4.52–4.61 (m, 1H), 4.02 (dd, $J = 11.6$, 4.4 Hz, 2H), 3.54 (t, $J = 11.6$ Hz, 2H), 2.58 (s, 3H), 2.37 (qd, $J = 12.4$, 4.4 Hz, 2H), 1.79 (dd, $J = 12.4$, 2.4 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 151.4, 142.8, 133.5, 121.3, 120.9, 118.6, 111.5, 66.6, 52.3, 30.7, 14.6. Mp: 167–171°C. Anal. calc. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.30; H, 7.43; N, 12.97. HRMS: calc. for $C_{13}H_{17}N_2O$: 217.1341. Found 217.1339.

2-Methyl-1-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-benzimidazole **(4c)**: ^{1}H NMR (DMSO-d_6): δ 8.00–8.03 (m, 1H), 7.78–7.80 (m, 1H), 7.52–7.55 (m, 2H), 4.67 (m, 1H), 2.99 (t, $J = 12.0$ Hz, 2H), 2.87 (s, 3H), 2.79 (d, $J = 12.0$ Hz, 2H), 2.43 (qd, $J = 12.8$, 3.2 Hz, 2H), 2.31 (dd, $J = 12.8$, 3.2 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 151.1, 130.5, 130.1, 125.5, 125.3, 114.2, 114.2, 56.2, 31.5, 27.5, 12.5. Mp: 270°C dec. Anal. calc. for $C_{13}H_{17}ClN_2S$: C, 58.09; H, 6.37; N, 10.42. Found: C, 58.09; H, 6.42; N, 10.39. HRMS: calc. for $C_{13}H_{17}N_2S$: 233.1112. Found 233.1106.

2-Methyl-1-(1,2,3,4-tetrahydro-2-naphthalenyl)-1*H*-benzimidazole **(7c)**: ^{1}H NMR (CD_2Cl_2): 7.64 (d, $J = 8.4$ Hz, 1H), 7.48 (d, $J = 6.8$ Hz, 1H), 7.21–7.14 (m, 6H), 4.75–4.66 (m, 1H), 3.65 (dd, 1H, $J = 16.4$, 11.6 Hz), 3.10 (m, 3H), 2.77–2.66 (m, 1H), 2.63 (s, 3H), 2.26–2.23 (m, 1H). ^{13}C NMR (CD_2Cl_2): 152.0, 144.0, 136.0, 135.0, 134.4, 129.7, 129.3, 126.9, 126.6, 122.0, 121.8, 119.7, 111.7, 53.8, 34.3, 30.2, 28.7, 15.4. HRMS: calc. for $C_{18}H_{19}N_2$: 263.1548. Found 263.1545.

2-Methyl-1-(1-phenylethyl)-1*H*-benzimidazole **(8c)**: ^{1}H NMR (CD_2Cl_2): 7.62 (d, 1H, $J = 10.0$ Hz), 7.33 (m, 3H), 7.23 (m, 2H), 7.14 (m, 1H), 7.04 (m, 2H), 5.78 (q, 1H, $J = 9.0$ Hz), 2.58 (s, 3H), 1.97 (d, 3H, $J = 9.0$ Hz). ^{13}C NMR (CD_2Cl_2): 152.2, 143.8, 140.4, 134.6, 129.2, 128.2, 126.9, 122.0, 121.8, 119.5, 111.6, 53.9, 18.8, 15.3. HRMS: calc. for $C_{16}H_{17}N_2$: 237.1392. Found 237.1394.

2-Methyl-1-[(2*E*)-1-methyl-3-phenyl-2-propen-1-yl]-1*H*-benzimidazole **(9c)**: ^{1}H NMR (CD_2Cl_2): 7.65 (m, 1H), 7.47 (m, 1H), 7.40–7.38 (m, 2H), 7.35–7.27 (m, 3H), 7.19 (m, 2H), 6.55 (s, 2H), 5.31 (q, 1H), 2.65 (s, 3H), 1.80 (d, $J = 8.5$ Hz, 3H). ^{13}C NMR (CD_2Cl_2): 151.8, 143.7, 136.7, 134.5, 131.8, 129.2, 129.1, 128.5, 126.9, 122.1, 121.9, 119.4, 111.8, 53.0, 19.2, 15.2.

ACKNOWLEDGMENTS

We gratefully acknowledge helpful discussions with Alan Millar, William J. Smith, Elie A. Tabet, and Shiping Xie.

REFERENCES

1. (a) Examples of benzimidazoles in active pharmaceutical ingredients include anti-secretory omeprazole (Prilosec), antihypertensive telmisartan (Micardis), and anthelminthic albendazole (Zentel); (b) Nishiyama, Y.; Fujimoto, M.; Sonoda, N. *Synlett* **2006**, 109, and references cited therein; (c) Preston, P. N. *The Chemistry of Heterocyclic Compounds: Benzimidazoles and Congeneric Tricyclic Compounds*; John Wiley & Sons: New York, vol. 40, 1980.
2. (a) Yang, D.; Fokas, D.; Li, J.; Yu, L.; Baldino, C. M. *Synthesis* **2005**, *1*, 47; (b) Rueckle, T.; Biamonte, M.; Grippi-Valloton, T.; Arkinstall, S.; Cambet, Y.; Camps, M.; Chabert, C.; Church, D. J.; Halazy, S.; Jiang, X.; Martinous, I.; Nichols, A.; Sauer, W.; Gotteland, J.-P. *J. Med. Chem.* **2004**, *47*, 6921; (c) Wu, Z.; Rea, P.; Wickahm, G. *Tetrahedron Lett.* **2000**, *41*, 9871; (d) Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, S. T.; Thomason, D. A. *J. Med. Chem.* **1992**, *35*, 377.
3. (a) Lin, S.-Y.; Isome, Y.; Stewart, E.; Liu, J.-F.; Yohannes, D. *Tetrahedron Lett.* **2006**, *47*, 2883, and references cited therein; (b) Wright, J. B. *Chem. Rev.* **1951**, *48*, 397; (c) Preston, P. N. *Chem. Rev.* **1974**, *74*, 279; (d) Gray, D. N. J. *Heterocycl. Chem.* **1970**, *7*, 947; (e) Hudkins, R. L. *Heterocycles* **1995**, *41*, 1045; (f) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893; (g) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814; (h) Howarth, J.; Hanlon, K. *Tetrahedron Lett.* **2001**, *42*, 751; (i) Hendrickson, J. B.; Hussoin, S. M. *J. Org. Chem.* **1989**, *54*, 1144.
4. Salehi, P.; Dabiri, M.; Zolfigol, M.; Otokesh, S.; Baghbanzadeh, M. *Tetrahedron Lett.* **2006**, *47*, 2557.
5. DiCesare, J. C.; White, C. E.; Rasmussen, W. E.; White, B. M.; McComas, C. B.; Craft, L. E. *Synth. Commun.* **2005**, *35*, 663.
6. McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307.
7. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
8. Paul, S. F. US Patent 5,697,987, December 16, **1997**.
9. Fitzpatrick, S. W. US Patent 4,897,497, January 30, 1990. Methyl tetrahydrofuran can be derived from cellulosic materials, including agricultural waste, coffee grounds, leaves, and sawdust, and can be blended with ethanol and alkanes to make homegrown transportation fuels. The MTHF–alkane mother liquors (filtrates and wash) are presumably suitable for direct recycling as transportation fuels.