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# FACILE PREPARATION OF SUBSTITUTED BENZIMIDAZOLE-2-CARBOXYLATES

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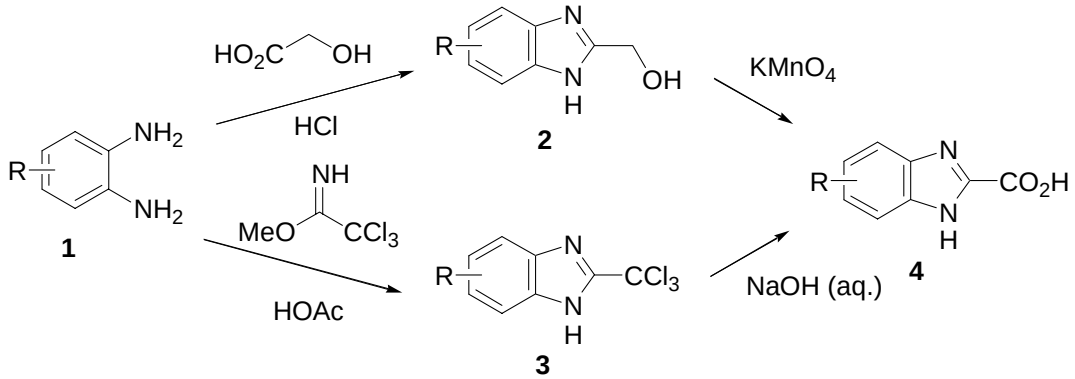
**Abstract** – Mild conditions for the preparation of benzimidazole-2-carboxylates have been developed. Condensation of a substituted 1,2-phenylenediamine with methyl trichloroacetamidate in the presence of TFA rapidly affords the 2-trichloromethylbenzimidazole; hydrolysis provides the desired product.

The benzimidazole-2-carboxamide moiety is a regular structural motif that appears in compounds possessing activity against a variety of important biological targets.[1] Most commonly, the carboxamides are prepared from the corresponding benzimidazole-2-carboxylates. As indicated in Scheme 1, two main routes have been described for preparation of these acids: i) condensation of the requisite 1,2-phenylenediamine (**1**) with glycolic acid, followed by $KMnO_4$ oxidation;[2] ii) condensation of **1** with methyl trichloroacetimidate in neat acetic acid, followed by NaOH hydrolysis to give **4**.[3] In the latter sequence, the intermediate (**3**) is typically isolated by crystallization prior to hydrolysis.

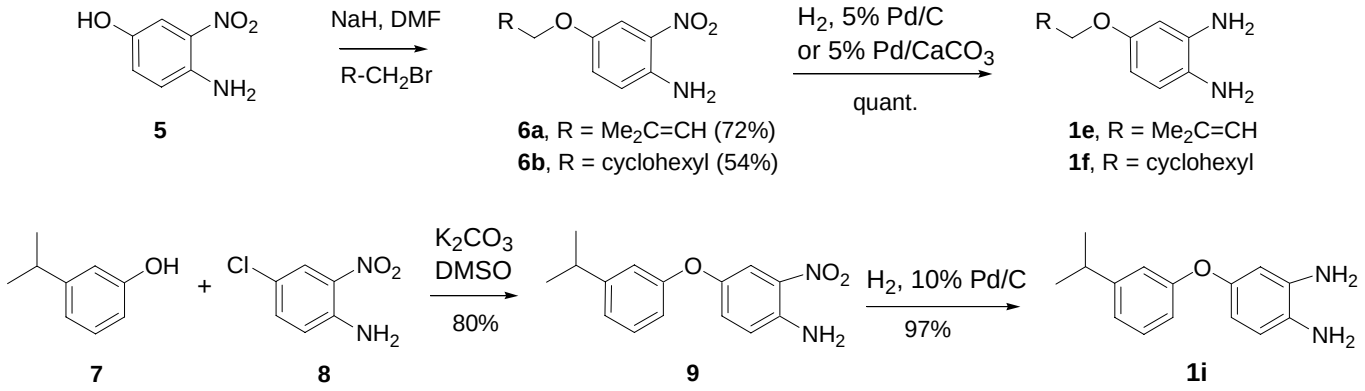



Scheme 1

Unfortunately, given the amphoteric nature of the functionality in **4**, isolation and handling of these materials tends to be problematic. More seriously, the reaction conditions themselves limit the scope of

acceptable substrates, both in terms of oxidative stability (glycolic acid route) and reactivity under mild acidic conditions (trichloroacetimidate route). As a result, relatively few examples of **4** have been described,[1-3] and most of these have contained simple alkyl, halo or nitro substituents on the benzimidazole ring.[1a, 1d, 2b, 3]

In the course of our medicinal chemistry program, we required a versatile and straightforward route to a series of substituted benzimidazole-2-carboxylates. Owing to the milder conditions of the trichloroacetimidate route, we chose to examine this chemistry in more detail with an emphasis on determining the general utility of this method. Substrates for this study were either known compounds or were prepared as indicated below (Scheme 2). Thus, alkylation of **5** with 4-bromo-2-methyl-2-butene and (bromomethyl)cyclohexane, followed by reduction of nitro groups in the presence of Pd(0) afforded **1e** and **1f**, respectively. Similarly, reaction of **7** with **8** followed by reduction afforded the diamine (**1i**). The free 1,2-phenylenediamines prepared for this study were sensitive to air oxidation, and were used immediately in the following step.

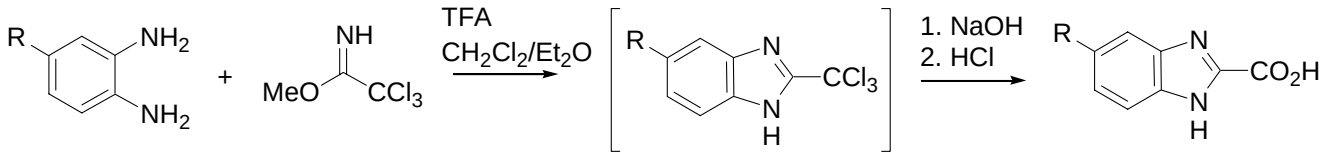



Scheme 2

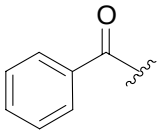
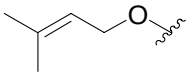
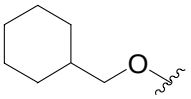
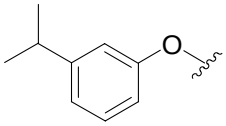
When we applied the literature conditions[3c] for the trichloroacetimidate condensation to our substrates, we observed sluggish reactions and low yields. We attributed this result to two factors: first, poor reactivity of **1** in the condensation with methyl trichloroacetimidate; second, intermediate (**3**) did not readily crystallize for lipophilic substrates, which necessitated removing the excess acetic acid at elevated temperature during which time decomposition of **3** was observed. Reasoning that a stronger acid in the condensation step should accelerate the formation of **3**, and that use of stoichiometric acid would preclude isolation of **3**, we repeated the sequence in $CH_2Cl_2/Et_2O$ using 2.5 equiv. of TFA. We were gratified to observe much faster reaction times and fewer side-products. Moreover, isolation of the intermediate (**3**) was not required, as this material could be directly hydrolysed with NaOH. The basic solution of the resulting acid (**4**) could then be washed with $CH_2Cl_2$ to remove any organic impurities, and the desired product precipitated from

dilute HCl solution. With these modified conditions in hand, we proceeded to apply them to substrates **1a-i** (Table 1).

Table 1. Conversion of 1,2-Phenylenediamines to Benzimidazole-2-carboxylates[a]




**1a-i** **3a-i** **4a-i**

| Entry | Substrate | Product | R | Isolated yield (%) |
|---|---|---|---|---|
| 1 | **1a** | **4a**[1a] | Me | 78 |
| 2 | **1b** | **4b**[1a] | $CF_3$ | 90 |
| 3 | **1c** | **4c** | *t*-Bu | 72 |
| 4 | **1d** | **4d**[1d] |  | 50 |
| 5 | **1e** | **4e** |  | 40 |
| 6 | **1f** | **4f** |  | 43 |
| 7 | **1g**[4] | **4g** | BnO | 32 |
| 8 | **1h**[5] | **4h** | PhO | 45 |
| 9 | **1i** | **4i** |  | 53 |

[a]All reactions were carried out on 2.0 mmol scale using the General Procedure described in the EXPERIMENTAL.

For substrates bearing simple alkyl substituents on the phenyl ring (**1a-c**), we obtained good to excellent yields of the corresponding benzimidazole-2-carboxylic acids (Entries 1-3). Lower yields were obtained in cases where the substituents included benzoyl, alkoxy and phenoxy groups (**1d-i**, Entries 4-9). The decreased yields may have been partially due to the higher organic solubility of the carboxylate salts of these substrates when the basic aqueous phase was washed with $CH_2Cl_2$ (see EXPERIMENTAL). However, since purification of the products (**4**) by chromatography is problematic, the washing step is required to remove any organic impurities.

It is important to note that the literature yields for **4a** and **4b** using the trichloroacetimidate method are 31% and 73%, respectively,[1a] while the literature yield for **4d** using the glycolic acid method is 29%.[1d] The

yields obtained using our procedure are substantially higher (Entries 1-2, 4). To check the reproducibility of our protocol on larger scale, we repeated the synthesis of **4a** using 4 g of substrate (**1a**); in this case, an 80% yield of product was obtained, demonstrating the suitability of these conditions for gram-scale synthesis. Owing to the low solubility of most products, it was necessary to acquire NMR spectra in DMSO-$d_6$. Under these conditions, all products exhibited tautomers which complicated the $^{13}$C NMR spectra. To confirm the presence of tautomers, we measured the $^{13}$C NMR spectra of products (**4f** and **4h**) at high temperature (65 ºC); as expected, the spectra simplified to a single set of signals consistent with our structural assignments.

In summary, we have developed a rapid, experimentally facile technique for the conversion of substituted 1,2-phenylenediamines to the corresponding benzimidazole-2-carboxylates. This method can be applied to a variety of structurally diverse substrates and is suitable for gram-scale synthesis.

## EXPERIMENTAL

All reactions were carried out under ambient conditions unless otherwise noted. Reagents were obtained from commercial sources and were used without further purification. $^1$H and $^{13}$C NMR experiments were performed on a Bruker Avance 300 spectrometer. NMR spectra were referenced to residual solvent ($^1$H and $^{13}$C with δ(TMS) = 0 ppm). MS spectra were obtained on a Bruker Esquire-LC 00052 mass spectrometer with an electrospray interface. Elemental analyses were performed at Atlantic Microlabs, Inc. Norcross, Georgia, USA.

**4-(3-Methyl-but-2-enyloxy)benzene-1,2-diamine (1e)**

To a 0 ºC solution of 4-amino-3-nitrophenol (**5**) (1.50 g, 9.73 mmol) in DMF (20 mL) was added 95% sodium hydride (280 mg, 11.6 mmol) in three portions. The red reaction mixture turned dark purple in colour. The mixture was warmed to room temperature and stirred for 15 m. 4-Bromo-2-methyl-2-butene (1.12 mL, 9.73 mmol) was added and the mixture was stirred for 1 h. Water was added slowly (6 mL) followed by brine (50 mL) and the mixture was extracted four times with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (EtOAc-hexanes 1:8) provided 1.56 g (72%) of **6a** as an orange solid. mp 85-86 ºC, recrystallized from hexanes. $^1$H NMR ($CDCl_3$) δ 1.76 (s, 3H), 1.80 (s, 3H), 4.48 (d, 2H, *J* = 6.6 Hz), 5.43-5.48 (m, 1H), 5.87 (br s, 2H), 6.74 (dd, 1H, *J* = 1.5, 10.5 Hz), 7.07 (dd, 1H, *J* = 2.2, 9.0 Hz), 7.57 (d, 1H, *J* = 2.4 Hz). $^{13}$C NMR ($CDCl_3$) δ 18.6, 26.2, 65.9, 107.7 119.5, 120.5, 127.8, 139.3, 140.3, 150.3. ES-MS *m/z* 245 (M+Na).

A mixture of the above amine (559 mg, 2.52 mmol) and 5% Pd with lead on $CaCO_3$ (100 mg) in methanol (20 mL) was subjected to hydrogenation at 35 psi for 1.5 h. The catalyst was filtered through a plug of

Celite, which was washed with methanol. The solution turned dark upon exposure to air and was concentrated to give **1e** as a dark black solid (483 mg). The diamine was used without purification.

**4-Cyclohexylmethoxybenzene-1,2-diamine (1f)**

To a 0 ºC solution of 4-amino-3-nitrophenol (**5**) (2.26 g, 14.6 mmol) in DMF (30 mL) was added 95% sodium hydride (422 mg, 11.6 mmol) in three portions. The red reaction mixture turned dark purple in color. The mixture was warmed to rt and stirred for 15 m. Bromomethylcyclohexane (2.23 mL, 16.1 mmol) was added and the mixture was heated at 90 ºC for 4 h. Water was added slowly (6 mL) followed by brine (50 mL) and the mixture was extracted four times with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (EtOAc-hexanes 1:10) provided 1.98 g (54%) of **6b** as an orange solid. mp 109-110 ºC, recrystallized from hexanes. $^1$H NMR ($CDCl_3$) δ 0.98-1.36 (m, 5H), 1.68-1.87 (m, 6H), 3.72 (d, 2H, *J* = 6.3 Hz), 5.86 (br s, 2H), 6.74 (d, 1H, *J* = 9.0 Hz), 7.07 (dd, 1H, *J* = 2.7, 9.0 Hz), 7.52 (d, 1H, *J* = 2.7 Hz). $^{13}$C NMR ($CDCl_3$) δ 26.2, 26.9, 30.2, 38.0, 74.6, 107.4, 120.4, 127.6, 140.3, 150.8, 200.3. ES-MS *m/z* 273 (M+Na). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.47; H, 7.28; N, 10.98.

A mixture of the above amine (587 mg, 2.35 mmol) and 10% Pd/C (60 mg) in methanol (20 mL) was subjected to hydrogenation at 40 psi for 1 h. The catalyst was filtered through a plug of Celite, which was washed with methanol. The solution turned dark upon exposure to air and was concentrated to give **1f** as a dark black solid (516 mg). The diamine was used without purification.

**4-(3-Isopropyl-phenoxy)benzene-1,2-diamine (1i)**

A mixture of 3-isopropylphenol (**7**) (2.04 g, 15.0 mml), 4-chloro-2-nitroaniline (**8**) (1.73 g, 10.0 mmol), and $K_2CO_3$ (2.07 g, 15.0 mmol) in DMSO (20 mL) was stirred at 140ºC overnight. After the mixture was cooled to rt, brine (50 mL) was added and the product was extracted with ether (3 × 50 mL). The combined extract was washed with water (50 mL), and dried over anhydrous $Na_2SO_4$. After filtration the solvent was removed under reduced pressure to give a dark brown residue. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$) to afford the yellow solid (**9**) (2.19 g, 80%). $^1$H NMR ($CDCl_3$) δ 1.26 (d, 6H, *J* = 6.9 Hz), 2.93 (septet, 1H, *J* = 6.9 Hz), 6.11 (br s, 2H), 6.15 (d, 1H, *J* = 2.7 Hz), 6.33 (dd, 1H, *J* = 2.7, 9.6 Hz), 6.86-6.91 (m, 1H), 6.94-6.96 (m, 1H), 7.11 (d, 1H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 7.8 Hz), 8.10 (d, 1H, *J* = 9.6 Hz).

Under $N_2$, to a hydrogenation flask, charged with 10% Pd/C (0.42 g), was added a solution of **9** (2.19 g, 8.04 mmol) in MeOH/EtOAc (30 mL, 1:1 v/v). The mixture was shaken under $H_2$ (40 psi) at rt overnight, then $CH_2Cl_2$ (20 mL) was added. After filtration through Celite the solvent was removed under reduced pressure to afford a dark brown residue. The residue was purified by flash chromatography on silica gel (EtOAc) to afford the yellow solid (**1i**) (1.89 g, 97%). $^1$H NMR ($CDCl_3$) δ 1.24 (d, 6H, *J* = 6.9 Hz), 2.87

(septet, 1H, *J* = 6.9 Hz), 3.24 (br s, 2H), 3.48 (br s, 2H), 6.39 (dd, 1H, *J* = 2.7, 8.1 Hz), 6.44 (d, 1H, *J* = 2.7 Hz), 6.67 (d, 1H, *J* = 8.1 Hz), 6.72-6.76 (m, 1H), 6.86-6.91 (m, 2H), 7.19 (t, 1H, *J* = 7.8 Hz).

**General Procedure**

To a solution of a substituted 1,2-phenylenediamine (2.00 mmol) in $CH_2Cl_2$/ether (25 mL, 2:3 v/v) was added methyl 2,2,2-trichloroacetimidate (441 mg, 2.50 mmol) followed by addition of TFA (385 μL, 5.00 mmol). The reaction mixture was stirred at rt for 2 h, and then filtered through filter paper. The residue on the paper was washed with $CH_2Cl_2$/diethyl ether (1:1 v/v). To the combined filtrate was added NaOH (1.5 N, 20 mL), and the organic solvent was removed. Mixed methanol/ether (20 mL, 1:1 v/v) was then added. The mixture stirred at rt overnight, and the filtrate was concentrated to remove the organic solvent. The aqueous residue was washed with dichloromethane (2 × 10 mL), and then filtered through a celite cake. The filtrate was then acidified with HCl (6 N) to afford the final product as a white crystalline solid, which was isolated by filtration and dried under reduced pressure (vacuum pump). Notably, the resulting products exhibited limited solubility in organic solvents and as a result, they were not recrystallized; however, good yields were obtained for subsequent EDCI couplings carried out in DMF (data not shown). The following products were obtained using the General Procedure, with the yields shown in Table 1:

**5-*tert*-Butyl-1*H*-benzoimidazole-2-carboxylic acid (4c)**

mp 143-145 ºC. $^1$H NMR ($CD_3OD$) δ 1.41 (s, 9H), 7.67-7.74 (m, 3H). $^{13}$C NMR (DMSO-$d_6$) (2 tautomers) δ 31.37, 31.67, 34.49, 34.75, 110.87, 114.92, 115.68, 120.14, 122.93, 124.27, 134.20, 135.37, 135.78, 137.10, 141.77, 145.06, 147.72, 158.72. ES-MS *m/z* 219 (M+H). Anal. Calcd for $C_{12}H_{14}N_2O_2 \cdot 0.7H_2O$: C, 62.43; H, 6.72; N, 13.13. Found: C, 62.24; H, 6.58; N, 12.24.

**5-(3-Methyl-but-2-enyloxy)-1*H*-benzoimidazole-2-carboxylic acid (4e)**

mp 146-147 ºC. $^1$H NMR (DMSO-$d_6$) δ 1.71 (s, 3H), 1.73 (s, 3H), 4.55 (d, 2H, *J* = 6.3 Hz), 5.40-5.44 (m, 1H), 6.95 (d, 1H, *J* = 10.3 Hz), 7.02 (s, 1H), 7.53 (d, 1H, J = 9.0 Hz). $^{13}$C NMR (DMSO-$d_6$) (2 tautomers) δ 23.6, 31.0, 70.4, 102.9, 103.9, 117.9, 121.0, 121.7, 123.3, 125.4, 125.9, 142.8, 149.2, 160.4, 162.1, 164.6. ES-MS *m/z* 247 (M+H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C,59.45; H,6.35; N,12.60. Found: C,59.71; H,6.43; N,12.62.

**5-Cyclohexylmethoxy-1*H*-benzoimidazole-2-carboxylic acid (4f)**

mp 137-139 ºC. $^1$H NMR (DMSO-$d_6$) δ 1.00-1.27 (m, 5H), 1.54-1.83 (m, 6H), 3.78 (d, 2H, *J* = 6.0 Hz), 6.95-6.99 (m, 2H), 7.52 (m, 1H). $^{13}$C NMR (DMSO-$d_6$, rt) (2 tautomers) δ 25.6, 26.4, 29.6, 37.5, 73.6, 97.3, 98.3, 112.9, 115.6, 116.4, 118.2, 132.5, 136.5, 141.4, 143.9, 157.3, 159.3. $^{13}$C NMR (DMSO-$d_6$, 65 ºC) δ 25.0, 25.8, 29.1, 36.9, 73.4, 98.5, 111.7, 115.8, 123.9, 132.8, 137.5, 140.9, 155.0. ES-MS *m/z* 275 (M+H). Anal. Calcd for $C_{15}H_{18}N_2O_3 \cdot 1.2H_2O$: C, 60.88; H, 6.95; N, 9.47. Found: C, 60.88; H, 6.78; N, 9.78.

**5-Benzyloxy-1*H*-benzoimidazole-2-carboxylic acid (4g)**

mp 151-152 ºC. $^1$H NMR (DMSO-$d_6$) δ 5.14 (s, 2H), 7.05 (dd, 1H, *J* = 1.8, 8.7 Hz), 7.11 (d, 1H, *J* = 1.8 Hz), 7.29 – 7.41 (m, 3H), 7.44 – 7.48 (m, 2H), 7.56 (d, 1H, *J* = 8.7 Hz). ES-MS *m/z* 269 (M+H).

**5-Phenoxy-1*H*-benzoimidazole-2-carboxylic acid (4h)**

mp 150-151 ºC. $^1$H NMR (DMSO-$d_6$) δ 6.99-7.15 (m, 5H), 7.35-7.40 (m, 2H), 7.66 (d, 1H, *J* = 8.7 Hz). $^{13}$C NMR (DMSO-$d_6$, rt) (2 tautomers) δ 105.2, 112.7, 114.7, 116.6, 117.6, 118.5, 122.2, 122.6, 123.5, 124.2, 124.7, 129.5, 129.9, 130.1, 135.3, 138.4, 142.8, 151.6, 154.6, 158.2. $^{13}$C NMR (DMSO-$d_6$, 65 ºC) δ 105.0, 114.3, 116.1, 117.1, 122.3, 123.9, 129.4, 135.0, 138.2, 142.3, 151.5, 157.9. ES-MS *m/z* 255 (M+H).

**5-(3-Isopropylphenoxy)-1*H*-benzoimidazole-2-carboxylic acid (4i)**

mp 142-143 ºC. $^1$H NMR (DMSO-$d_6$) δ 1.16 (d, 6H, *J* = 6.9 Hz), 2.86 (septet, 1H, *J* = 6.9 Hz), 6.76-6.79 (m, 1H), 6.92 (s, 1H), 6.99-7.10 (m, 3H), 7.25-7.30 (m, 1H), 7.65 (d, 1H, *J* = 8.7 Hz). ES-MS *m/z* 297 (M+H).

## REFERENCES


1. a) H.-P. Buchstaller, M. Wiesner, F. Zenke, C. Amendt, M. Grell, and C. Sirrenberg, PCT Int. Appl. 2005, WO 05004863. b) M. Nazare, M. Wagner, V. Wehner, H. Matter, M. Urmann, and K. Ritter, Eur. Pat. Appl. 2004, EP 1479676. c) G. Bridger, E. J. McEachern, R. Skerlj, and D. Schols, U.S. Pat. Appl. 2004, US 04209921. d) N. I. Carruthers, C. A. Dvorak, J. P. Edwards, C. A. Grice, J. A. Jablonowski, K. S. Ly, B. A. Pio, C. R. Shah, and J. D. Venable, PCT Int. Appl. 2004, WO 04022060. e) K. Kobayashi, H. Takahashi, H. Kawamoto, T. Kato, S. Itoh, T. Yoshizumi, and O. Okamoto, PCT Int. Appl. 2003, WO 03095432.
2. a) R .A. B. Copeland and A. R. Day, *J. Am. Chem. Soc.*, 1943, **65**, 1072. b) A. F. Crowther, F. H. S. Curd, D. G. Davey, and G. J. Stacey, *J. Chem. Soc.*, 1949, 1260.
3. a) N. Terzioglu, R. M. van Rijn, R. A. Bakker, I. J. P. De Esch, and R. Leurs, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5251. b) G. Dannhardt and B. K. Kohl, *Arch. Pharm. Pharm. Med. Chem.*, 2000, **333**, 123. c) P. Louvet, G. Lallement, I. Pernot-Marino, C. Luu-Duc, and G. Blanchet, *Eur. J. Med. Chem.*, 1993, **28**, 71.
4. P. Madsen, L. B. Knudsen, F. C. Wiberg, and R. D. Carr, *J. Med. Chem.*, 1998, **41**, 5150.
5. G. De Nanteuil, B. Portevin, J. Bonnet, and A. Fradin, Eur. Pat. Appl. 1998, EP 820990.