

A convenient two-step synthesis of 6-methylenesubstituted-4-trichloromethyl-2-methylsulfanyl pyrimidines

Niló Zanatta,* Darlene C. Flores, Claudia C. Madruga, Alex F. C. Flores, Helio G. Bonacorso and Marcos A. P. Martins

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97.105-900, Santa Maria, RS, Brazil

Received 14 September 2005; revised 7 November 2005; accepted 7 November 2005
Available online 28 November 2005

Abstract—This work reports a two-step synthetic strategy to obtain a series of 6-methylenesubstituted-4-trichloromethyl-2-methylsulfanylpyrimidines from the cyclization of 5-bromo-4-methoxy-1,1,1-trichloro-pent-3-en-2-ones with 2-methyl-2-pseudothiourea sulfate, followed by nucleophilic substitution of 6-bromomethyl-4-trichloromethyl-2-methylsulfanylpyrimidine with a series of nucleophiles. Alternative strategies to obtain 6-halomethyl-4-trichloro[fluoro]methyl-2-methylsulfanyl pyrimidines have been addressed.

© 2005 Elsevier Ltd. All rights reserved.

The halogenation of position-5 of pyrimidines and their nucleoside derivatives has been the subject of many studies mainly due to the elevated antiviral and anticancer activities exhibited by these compounds.¹ On the other hand, the functionalization of the position-6 of pyrimidines has been attracting much attention since compounds such as HEPT and DABOs showed important anti-HIV-1 activity^{2,3} and structurally related pyrimidines exhibited antirubella virus activity⁴ (Fig. 1).

It is well known that the presence of halogenated groups in organic molecules often confer significant and useful changes in their chemical, physical, and biological properties due to the elevated electronegativity and lipophilic character of halogen atoms.^{5,6} As a consequence, in recent years much attention has been devoted to the synthesis of trifluorinated compounds and many have proven to be of important therapeutic value.^{7,8} Trichloromethyl substituted heterocycles have been the subject of fewer studies, however, recent investigations have shown that these compounds exhibited better pharmacological activities than the trifluorinated analogues.^{9–12}

Recently, a series of 6-methylpyridinium-pyrimidino-diones, which has been tested for its thymidine phosphorylase inhibitory activity, was obtained in a five-step synthesis from the commercially available 6-methyluracil.¹³ Considering the general interest of 6-methylenesubstituted-4-trihalomethylpyrimidines as potential probes for biological activity, in this work we show a two-step synthetic strategy to obtain a series of 6-methylenesubstituted-4-trichloromethyl-2-methylsulfanyl-pyrimidines. The most obvious approach to functionalize the 6-methylpyrimidine position is, first, to halogenate the methyl group of **1**¹⁴ (Scheme 1), followed by the nucleophilic substitution of the methylene-halogen by nucleophiles.

However, several tested methods for chlorination and bromination of 6-methyl-4-trichloro-2-methylsulfanyl pyrimidine (**1**), using many conditions and molar ratio of reagents, according to methods described in the literature,^{15–17} have always resulted in mixtures of mono-halogenated pyrimidine **2**, dihalogenated pyrimidine **3**, and starting material **1** in various proportions depending on the conditions and molar ratio of the reagents. These mixtures were difficult to separate by means of recrystallization or column chromatography. The tentative to halogenate the methyl group using *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) has also failed because these reactions require a catalytic amount of a peroxide to initiate the radical reaction.

Keywords: Pyrimidines; Enones; Halogenated heterocycles.

*Corresponding author. Tel./fax: +55 55 3220 8756; e-mail: zanatta@base.ufsm.br

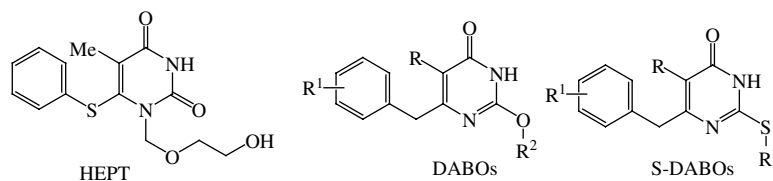
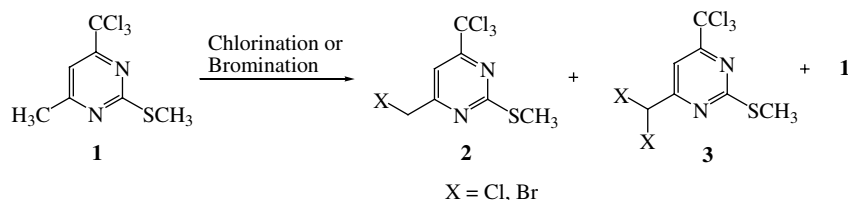


Figure 1. Structure of pharmacological active 6-substituted pyrimidines.

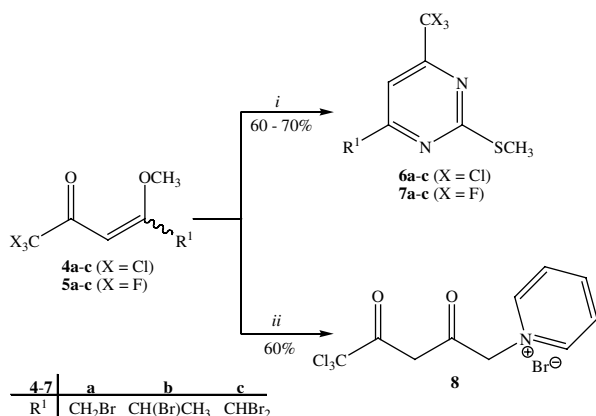


Scheme 1.

The peroxide, however, induced oxidation on the methylsulfanyl group of **1** giving a mixture of 2-methanesulfinyl and 2-methanesulfonyl derivatives together with starting material, instead of the desired methyl-halogenated products.

Since the direct halogenation of the 6-methyl-pyrimidine derivatives did not furnish the desired products, we used the halogen-containing building block approach for the synthesis of the title compounds. As a part of our research program, we developed a general synthesis of 5-bromo-1,1,1-trichloro-4-methoxy-3-pentene[hexen]-2-ones and demonstrated its usefulness for the synthesis of a series of 5-trichloromethyl-5-hydroxy-3-heteroalkyl-4,5-dihydroisoxazoles.¹⁸ It has been shown that the most convenient method to construct halogenated compounds is to use halogen-containing building blocks as the starting reagents.¹⁹ This method uses as starting material (building blocks), which are aliphatic compounds bearing halogens (compounds **4a–c** and **5a–c**)¹⁸ that will remain on the desired position in the final heterocycle (Scheme 2).

From the synthetic strategy presented in Scheme 2, pure monobrominated pyrimidines **6a–b** and **7a–b** and dibro-

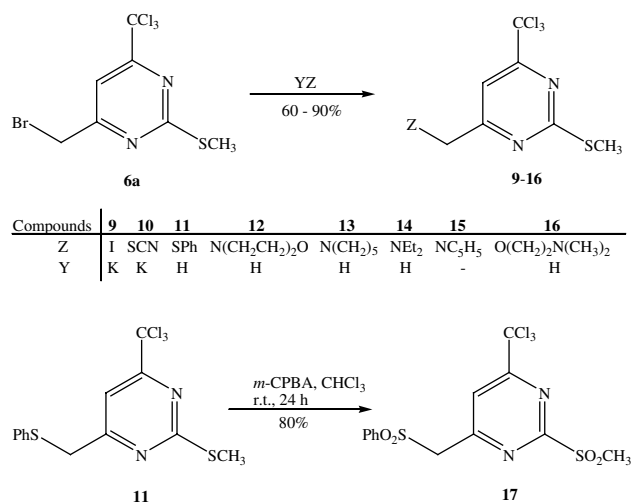


Scheme 2. Reagents and conditions: (i) 2-methyl-2-pseudothiourea sulfate, MeOH/H₂O (3:1), HCl, reflux, 48 h; (ii) 2-methyl-2-pseudothiourea sulfate, MeOH/H₂O (3:1), C₆H₅N, rt, 16 h.

minated pyrimidines **6c** and **7c** were obtained in 60–70% yield. The reaction to obtain compounds **6** and **7** were carried out by reacting the enones **4** or **5** with 2 equiv of 2-methyl-2-pseudothiourea sulfate in methanol/water (3:1 v/v) in the presence of hydrochloric acid. An unexpected β-dicarbonyl pyrimidinium salt **8** was obtained when compound **4a** was reacted with 2-methyl-2-pseudothiourea sulfate in the same solvent as above, but in the presence of pyridine instead of hydrochloric acid. Nucleophilic substitution of the bromine of compound **6a** by a series of nucleophiles furnished compounds **9–16** in good yields (Scheme 3).

This series of nucleophiles has been selected in order to demonstrate the synthetic versatility of compounds **6** or **7** to establish new carbon–halogen, carbon–sulfur, carbon–nitrogen, and carbon–oxygen bonds. Here, only compound **6a** was tested since CCl₃ group is more labile than CF₃ group and, therefore, more susceptible to undergo undesired reactions.

Compounds **9** and **10** were obtained from the reaction of pyrimidine **6a** with 2 equiv of potassium iodide and potassium thiocyanate, respectively, in acetone at



Scheme 3.

25 °C, for 8 h. Compounds **9** and **10** were obtained as dark solids and were recrystallized from a mixture of hexane/ethyl acetate to give white solids in good yields. Compound **11** was obtained from the reaction of **6a** with 2 equiv of thiophenol and triethylamine in benzene for 8 h at 40 °C. Compounds **12–14** were obtained from the reaction of **6a** with 2 equiv of morpholine, piperidine, and diethylamine, respectively, in dry acetone for 16 h at room temperature. An excess of the nucleophiles (e.g., 2:1) was used to improve yields. When the reaction of the pyrimidine **6a** with amines was carried out in the same molar ration, in the presence of triethylamine, lower yields were obtained and impurities were observed. Compound **15** was obtained by stirring the pyrimidine **6a** with pyridine, used as solvent, at room temperature for 48 h. Compound **15** was isolated by precipitation in dichloromethane and analyzed without further purification. Compound **16** was obtained by stirring the pyrimidine **6a** with 2 equiv of 2-dimethylaminoethanol in acetone, at room temperature for 4 h. Compound **11** was oxidized with 3-chloroperoxybenzoic acid in chloroform to give the disulfonyl **17** in good yields. All compounds were analyzed by ¹H and ¹³C NMR, GC–MS, and some representative compounds, also by elemental analysis.²⁰

In summary, this work showed a simple and efficient method to obtain the title compounds in two reaction steps from the halogenated building block approach. This method shows a clear advantage over the method reported in the literature where the synthesis of 6-methylenesubstituted uracil derivatives was obtained in five reaction steps starting from the 6-methyl uracil.¹³ This work also showed that the direct halogenation of the pyrimidine side methyl group led to a mixture of mono- and dihalogenated compounds of difficult separation and, therefore, of limited use to obtain the title compounds.

Acknowledgements

The authors thank the financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico—CNPq (Universal Grant No. 477682/01-4), fellowships (D.C.F.), and fellowships from CAPES (C.C.M.).

References and notes

- Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Pergamon Press: NY, 1980; Vol. 2, p 79; Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Pergamon Press: NY, 1980; Vol. 3, p 152.
- Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357–8367.
- Garg, R.; Gupta, S. P.; Gao, H.; Babu, M. S.; Debnath, A. K.; Hansch, C. *Chem. Rev.* **1999**, *99*, 3525–3601.
- Botta, M.; Occhionero, F.; Nicoletti, R.; Mastromarino, P.; Conti, C.; Magrini, M.; Saladino, R. *Bioorg. Med. Chem.* **1999**, *7*, 1925–1931.
- Filler, R.; Kobayashi, Y.; Yagupolski, L. M. *Fluorine in Biorganic Chemistry*; Elsevier: Amsterdam, 1993.

- Hudlicky, M. *Chemistry of Organofluorine Compounds*; Ellis Horwood: Chichester, 1992.
- Pierce, M. E.; Parsons, R. L.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grobowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536–8543.
- Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197.
- Souza, F. R.; Figuera, M. R.; Lima, T. T. F.; Bastiani, J.; Barcellos, I. B.; Almeida, C. E.; Oliveira, M. R.; Bonacorso, H. G.; Flores, A. E.; Mello, C. F. *Pharmacol., Biochem. Behav.* **2001**, *68*, 525–530.
- Schetinger, M. R. C.; Porto, N. M.; Moretto, M. B.; Morsch, V. M.; Rocha, J. B. T.; Vieira, V.; Moro, F.; Neis, R. T.; Bittencourt, S.; Bonacorso, H. G.; Zanatta, N. *Neurochem. Res.* **2000**, *25*, 949–955.
- Rubin, M. A.; Albach, C. A.; Berlese, D. B.; Bonacorso, H. G.; Bittencourt, S. R. T.; Queiroz, C. M. T.; Maixner, A. E.; Mello, C. F. *Braz. J. Med. Biol. Res.* **2000**, *33*, 1069–1073.
- Souza, F. R.; Souza, V. T.; Ratzlaff, V.; Borges, L. P.; Oliveira, M. R.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P.; Mello, C. F. *Eur. J. Pharmacol.* **2002**, *451*, 141–147.
- Murray, P. E.; McNally, V. A.; Lockyer, S. D.; Williams, K. J.; Stratford, I. J.; Jaffar, M.; Freeman, S. *Bioorg. Med. Chem.* **2002**, *10*, 525–530.
- Zanatta, N.; Madruga, C. C.; Clerice, E.; Martins, M. A. P. *J. Heterocycl. Chem.* **1995**, *32*, 735–738.
- Gershon, H.; Grefig, A. T.; Scala, A. A. *J. Heterocycl. Chem.* **1983**, 219–224.
- Strekowski, L.; Wydra, R. L.; Jandra, L.; Harden, D. B. *J. Org. Chem.* **1991**, *56*, 5610–5614.
- Badawey, E.-S. A. M. *J. Heterocycl. Chem.* **1996**, 1003–1015.
- Martins, M. P. P.; Sinhoin, A. P.; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P. *Synthesis* **2001**, 1959–1964.
- Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Sinhoin, A. P.; Flores, A. F. C.; Bonacorso, H. G.; Zanatta, N. *Curr. Org. Synth.* **2004**, *1*, 391–403.
- Physical and spectral data of selected compounds:
Compound **6a**: Yield 60%. δ_{H} (400 MHz, CDCl₃): 2.62 (s, 3H, SCH₃), 4.52 (s, 2H, CH₂Br), 7.80 (s, 1H, H-5); δ_{C} (100 MHz; CDCl₃): 14.3 (SCH₃), 50.0 (CH₂Br), 95.5 (CCl₃), 108.7 (C5), 167.0 (C4), 167.9 (C2), 173.3 (C6). GC–MS (EI, 70 eV) m/z (%): 334 (M⁺, 1), 290 (30), 255 (100), 219 (40).
Compound **6b**: Yield 70%; mp 54–57 °C (hexane). δ_{H} (400 MHz; CDCl₃): 1.83 (d, 3H, CH₃), 2.62 (s, 3H, SCH₃), 5.03 (qua, 1H, CH), 7.77 (s, 1H, H5). δ_{C} (100 MHz; CDCl₃): 14.3 (SCH₃), 24.2 (CH₃), 57.1 (CHBr), 94.5 (CCl₃), 107.6 (C5), 166.9 (C4), 171.8 (C2), 173.2 (C6). GC–MS (EI, 70 eV) m/z (%): 304 (M⁺–44, 29) 269 (100), 233 (71).
Compound **6c**: Yield 65%. δ_{H} (400 MHz; CDCl₃): 2.54 (s, 3H, SCH₃), 6.50 (s, 2H, CHBr₂) 7.60 (s, 1H, H-5). δ_{C} (100 MHz; CDCl₃): 14.3 (SCH₃), 69.3 (CHBr₂), 95.1 (CCl₃), 107.1 (C5), 167.9 (C4), 168.5 (C2), 173.6 (C6). GC–MS (EI, 70 eV) m/z (%): 254 (M⁺–158, 100), 219 (32).
Compound **7a**: Yield 60%. δ_{H} (400 MHz; CDCl₃): 2.61 (s, 3H, SCH₃), 4.62 (s, 2H, CH₂Br), 7.50 (s, 1H, H5). δ_{C} (100 MHz; CDCl₃): 14.0 (SCH₃), 44.7 (CH₂Br), 109.6 (C-5, ⁴J_{C-F} = 2.6), 120.3 (CF₃, ¹J_{C-F} = 285.0 MHz), 156.7 (C-4, ²J_{C-F} = 36.0 MHz), 167.8 (C2), 174.3 (C6). GC–MS (EI, 70 eV) m/z (%): 207 (M⁺–79, 100), 196 (10), 136 (25).

Compound **7b**: Yield 60%. δ_{H} (400 MHz; CDCl_3): 1.77 (t, 3H, CH_3), 2.51 (s, 3H, SCH_3), 4.92 (1H, q, CHBr), 7.40 (s, 1H, H5); δ_{C} (100 MHz; CDCl_3): 14.0 (SCH_3), 24.2 (CH_3), 56.9 (CHBr), 108.8 (q, $^4J_{\text{C-F}} = 2.6$ Hz, C-5), 120.3 (q, $^1J_{\text{C-F}} = 285$ Hz, CF_3), 156.7 (q, $^2J_{\text{C-F}} = 36$ Hz, C-4), 171.9 (C2), 174.2 (C6). GC–MS (EI, 70 eV) m/z (%): 221 ($\text{M}^+ - 79$, 100), 256 (44), 150 (27).

Compound **7c**: Yield 60%. δ_{H} (400 MHz; CDCl_3): 2.54 (s, 3H, SCH_3), 6.50 (s, 1H, CHBr_2), 7.60 (s, 1H, H5). δ_{C} (100 MHz; CDCl_3): 14.4 (SCH_3), 69.3 (CHBr_2), 108.3 (C-5), 120.1 (q, $^1J_{\text{CF}} = 235$ Hz, CF_3), 157.6 (q, $^2J_{\text{CF}} = 36$ Hz, C-4), 168.1 (C-2), 174.8 (C-6).

Compound **9**: Yield 90%; mp 180–185 °C. Found: C, 22.21; H, 1.64; N, 7.36. $\text{C}_7\text{H}_6\text{Cl}_3\text{IN}_2\text{S}$ requires C, 21.53; H, 1.58; N, 7.31. δ_{H} (400 MHz; CDCl_3): 2.56 (s, 3H, SCH_3), 4.85 (s, 2H, CH_2I), 7.80 (s, 1H, H-5). δ_{C} (100 MHz; CDCl_3): 3.8 (CH_2I), 13.5 (SCH_3), 94.9 (CCl_3), 109.1 (C5), 165.4 (C4), 171.1 (C2), 172.1 (C6). GC–MS (EI, 70 eV) m/z (%): 255 ($\text{M}^+ - 127$, 56), 220 (100), 185 (30).

Compound **10**: Yield 80%; mp 101–103 °C. Found: C, 30.79; H, 2.02; N, 13.50. $\text{C}_8\text{H}_6\text{Cl}_3\text{N}_2\text{S}_2$ requires C, 30.54; H, 1.92; N, 13.35. δ_{H} (400 MHz; CDCl_3): 7.95 (s, 1H, H5), 4.59 (s, 2H, CH_2SCN), 2.64 (s, 3H, SCH_3). δ_{C} (100 MHz; CDCl_3): 13.7 (SCH_3), 37.1 (CH_2SCN), 95.0 (CCl_3), 110.0 (C5), 112.4 (SCN), 165.6 (C4), 168.0 (C2), 172.6 (C6). GC–MS (EI, 70 eV) m/z (%): 313 (M^+ , 15), 298 (40), 278 (75), 255 (30), 219 (100).

Compound **11**: Yield 60%. δ_{H} (400 MHz; CDCl_3): 2.55 (s, 3H, SCH_3), 4.13 (s, 2H, CH_2SPh), 7.43 (s, 1H, H-5), 7.37–7.16 and 7.51–7.45 (m, 5H, SPh). δ_{C} (100 MHz; CDCl_3): 14.2 (SCH_3), 40.4 (CH_2SPh), 95.6 (CCl_3), 109.3 (C5), 127.3–133.9 (SPh), 166.0 (C4), 169.4 (C2), 173.0 (C6). GC–MS (EI, 70 eV) m/z (%): 364 (M^+ , 85), 349 (45), 329 (45), 219 (73), 109 (100).

Compound **12**: Yield 60%; mp 85–88 °C. Found: C, 36.28; H, 2.64; N, 6.49. $\text{C}_{11}\text{H}_{14}\text{Cl}_3\text{N}_3\text{OS}$ requires C, 36.34; H, 2.58; N, 6.52%. δ_{H} (400 MHz; CDCl_3): 2.77–2.66 (m, 4H, NCH_2), 2.62 (s, 3H, SCH_3), 3.77–3.66 (s, 4H, OCH_2), 7.76

(s, 1H, H-5). δ_{C} (100 MHz; CDCl_3): 14.2 (SCH_3), 53.6 (NCH_2), 66.7, 63.6 (OCH_2), 95.5 (CCl_3), 109.5 (C5), 166.3 (C4), 170.5 (C2), 173.0 (C6). GC–MS (EI, 70 eV) m/z (%): 255 ($\text{M}^+ - 86$, 65), 221 (55), 86 (100).

Compound **13**: Yield 60%; mp 85–88 °C. δ_{H} (400 MHz; CDCl_3): 1.39–1.40 (m, 2H, piperidine), 1.53–1.57 (m, 4H, piperidine), 2.38–2.40 (m, 4H, piperidine), 2.54 (s, 3H, SCH_3), 3.55 (s, 2H, CH_2), 7.70 (s, 1H, H5). δ_{C} (100 MHz; CDCl_3): 14.3 (SCH_3), 22.6, 24.5, 54.8 (piperidine), 63.9 (CH_2), 95.9 (CCl_3), 109.0 (C5), 166.0 (C4), 171.9 (C2), 172.6 (C6). GC–MS (EI, 70 eV) m/z (%): 303 ($\text{M}^+ - 36$, 25), 256 (42), 221 (54), 84 (100).

Compound **14**: Yield 60%. δ_{H} (400 MHz; CDCl_3): 1.10 (t, 6H, 2 CH_3), 2.61 (m, 4H, 2 CH_2), 2.54 (s, 3H, SCH_3), 3.66 (m, 2H, CH_2), 7.77 (s, 1H, H5). δ_{C} (100 MHz; CDCl_3): 11.9 (CH_3), 14.2 (SCH_3), 47.8 (2 CH_2), 58.5 (CH_2), 96.0 (CCl_3), 109.9 (C5), 166.0 (C4), 173.1 (C6), 172.4 (C2). GC–MS (EI, 70 eV) m/z (%): 256 ($\text{M}^+ - 71$, 50), 221 (46), 72 (100).

Compound **15**: Yield 80%; mp > 250 °C. δ_{H} (400 MHz; CDCl_3): 2.25 (s, 3H, SCH_3), 6.34 (s, 2H, CH_2), 8.15 (s, 1H, H-5), 8.27 (t, 2H, $^3J = 7.5$ Hz, pyridine), 8.74 (t, 2H, $^3J = 7.5$ Hz, pyridine) 9.30 (d, 2H, $^3J = 5.6$ Hz, pyridine). δ_{C} (100 MHz; CDCl_3): 13.64 (SCH_3), 62.6 (CH_2), 95.0 (CCl_3), 109.3 (C5), 127.8, 135, 146.6 (pyridine), 165.2 (C4), 166.0 (C2), 172.3 (C6).

Compound **16**: Yield 80%; mp 148–151 °C. δ_{H} (400 MHz; CDCl_3): 2.60 (s, 3H, SCH_3), 3.28 (s, 6H, NMe_2), 3.63 (t, 2H, CH_2), 3.93 (t, 2H, CH_2), 4.93 (s, 2H, CH_2), 8.20 (s, 1H, H-5); δ_{C} (100 MHz; CDCl_3): 14.0 (SCH_3), 51.5 (Me_2N), 54.9 (CH_2), 65.3, 66.1 (2 CH_2), 95.0 (CCl_3), 114.1 (C5), 162.0 (C4), 166.0 (C2), 172.6 (C6). GC–MS (EI, 70 eV) m/z (%): 255 ($\text{M}^+ - 88$, 100), 219 (40).

Compound **17**: Yield 80%; mp 178–183 °C. δ_{H} (400 MHz; CDCl_3): 3.25 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 7.59, 7.81 (m, 5H, Ph), 8.41 (s, 1H, H5); δ_{C} (100 MHz; CDCl_3): 40.0 (CH_3), 62.5 (CH_2), 93.9 (CCl_3), 121.3 (C5), 127.0, 128.9, 129.0, 137.9 (Ph), 164.9 (C2), 166.3 (C4), 166.5 (C6).