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Concurrent synthesis of vanillin and isovanillin

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Abstract A method for concurrent synthesis of vanillin and isovanillin has been developed by a nonregioselective Vilsmeier–Haack reaction of *O*-alkyl guaiacols. *O*-Alkylation of guaiacol provided the corresponding *O*-alkyl guaiacol (**1**), which was then formylated with *N*-methylformanilide/phosphorus oxychloride to give a mixture of 4-alkoxy-3-methoxy-benzaldehyde (**2**) and 3-alkoxy-4-methoxybenzaldehyde (**3**). Finally, the obtained mixture underwent a selective dealkylation by anhydrous aluminium trichloride, while leaving methyl groups intact to simultaneously achieve the significant fine chemicals vanillin and isovanillin.

Keywords Concurrent synthesis · Vanillin · Isovanillin · Vilsmeier–Haack reaction · Selective dealkylation

Introduction

Both vanillin and isovanillin are significant and indispensable organic compounds in the pharmaceutical, perfumery and flavor industry [1]. Most vanillin and isovanillin are primarily produced via synthetic methods. In particular, the annual production of vanillin is currently estimated to be over 15,000 t. Therefore, the synthesis of vanillin and isovanillin has always gained continuous attention in academia and industry. At the present times, Li et al. [2] reported an enzymatic synthesis of vanillin from glucose, and Bjørsvik et al. [3] also developed a chemical synthesis of vanillin by oxidation of lignosulfonates. On the other hand, Wang et al. [4] described a mild efficient Mitsunobu protocol for the regioselective alkylation of

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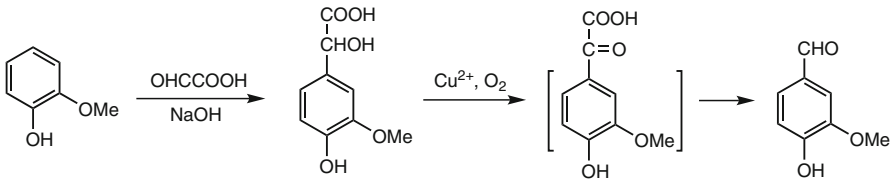


Scheme 1 Industrial process for synthesis of vanillin

3,4-dihydroxybenzaldehyde to prepare isovanillin, and Bao et al. [5] undertook an efficiently solvent-free debenzylation to obtain isovanillin using magnesium iodide.

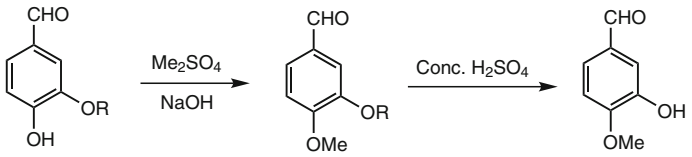
Condensation of guaiacol with glyoxylic acid followed by oxidation–decarboxylation is currently the major commercial route to vanillin (Scheme 1). Umemura [6] described a procedure to prepare vanillin, therein the condensation of guaiacol with glyoxylic acid in basic medium provided the intermediate 4-hydroxy-3-methoxymandelic acid, from which subsequent oxidation–decarboxylation was conducted with air using cupric catalyst. As to isovanillin, the main industrial process encompassed an inevitable dealkylation of 3-alkoxy-4-methoxybenzaldehyde with large amounts of concentrated sulphuric acid (Scheme 2) [7, 8].

The chemical introduction of an aldehyde group on aromatic nucleus can be delivered by many means, including direct methods (e.g., Gattermann reaction, Reimer–Tiemann reaction, Duff reaction, and Vilsmeier–Haack reaction) and indirect methods (whereby the group on aromatic nucleus converted into aldehyde group mainly by oxidation or reduction) [9]. It should be noted that Vilsmeier–Haack reaction for attachment of formyl group is superior to other direct methods in terms of yield, simplicity, and practicality. For example, by formylation with *N*-methylformanilide/phosphorus oxychloride, the availability of recyclable *N*-methylaniline generated from *N*-methylformanilide enables economical preparation of veratraldehyde from veratrole [10].

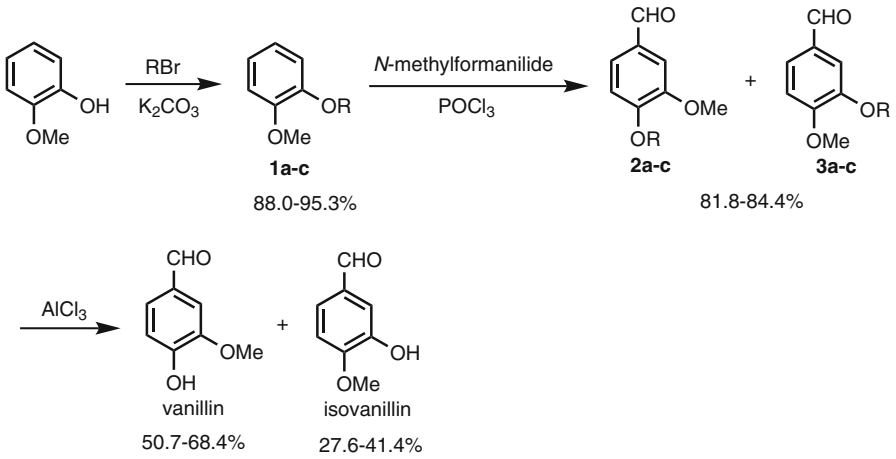
In this study, we developed a method for concurrent synthesis of vanillin and isovanillin by a nonregioselective Vilsmeier–Haack reaction of *O*-alkyl guaiacols (Scheme 3). *O*-Alkylation of guaiacol provided the corresponding *O*-alkyl guaiacol (**1**), which was formylated with *N*-methylformanilide/phosphorus oxychloride to give a mixture of regioisomeric 4-alkoxy-3-methoxybenzaldehyde (**2**) and 3-alkoxy-4-methoxybenzaldehyde (**3**). Accordingly, the resulting mixture underwent an efficient selective dealkylation by anhydrous aluminium trichloride, while leaving methyl groups intact to simultaneously achieve the desired fine chemicals vanillin and isovanillin.

Results and discussion

According to generally reported methods [11, 12], compounds **1** were synthesized by alkylation of guaiacol with alkyl bromide in excellent yields of 88.0–95.3 %. Individually, in the presence of potassium carbonate, guaiacol was alkylated with *n*-propyl bromide for 10 h to give the corresponding **1a** in 95.3 % yield, or with *n*-butyl bromide for 15 h to give the corresponding **1c** in 94.4 % yield. While the



Scheme 2 Industrial process for synthesis of isovanillin. R = Me, Et



Scheme 3 Concurrent synthesis of vanillin and isovanillin. a: R = *n*-Pr; b: R = *i*-Pr; c: R = *n*-Bu

treatment of guaiacol with *i*-propyl bromide in similar conditions for 24 h provided **1b** in relatively low yield of 88.0 % due to slightly greater steric hindrance of *i*-propyl group.

In the investigation of Vilsmeier–Haack reaction of *O*-alkyl guaiacols **1** with *N*-methylformanilide/phosphorus oxychloride, the gained products accounted for good yields of 81.8–84.4 %. Although the resultant **2** and **3** were not visibly distinguished by GC analysis, ^{1}H NMR, ^{13}C NMR and HPLC tests unambiguously demonstrated that the formylation reaction simultaneously achieved the two regioisomers, resulting from nonregioselective attack of electrophilic formyl group on *para*-position to either of the two alkoxy groups. ^{1}H NMR analysis further proved that each *para*-product **2** (to OR) possesses more quantity than the corresponding concomitant **3**, and the ratios of **2/3** are consistent with that of methoxy/alkoxy group of the Taft's substituent electric parameter σ^* values [13, 14] albeit the correlation is a little poor. The Taft's parameter σ^* was revised to solve the shortcoming of the Hammett constant σ. Here, *i*-propoxy group has the strongest electron-donating ability with the lowest Taft's σ^* value, but methoxy group was the opposite. The results of the formylation of aryl diethers **1** are summarized in Table 1. Indeed, the determined ratios of **2** and **3** met the final results of vanillin and isovanillin well (Table 2). Thus, the nonregioselective formylation of **1** accomplished a synchronous synthesis of two regioisomeric aldehydes **2** and **3**, and accordingly led to the desired vanillin and isovanillin.

Table 1 Results of the formylation of *O*-alkyl guaiacols **1**

[a] Combined isolated yield of **2** and **3**

[b] Determined by ^{1}H NMR analysis

OR	σ* [14]	Yield (%)[a]	Ratio (**2**/**3**)[b]
OMe	1.77	–	1/1 (**2** = **3**)
n-PrO (**1a**)	1.57	81.8	1.24/1
i-PrO (**1b**)	1.51	84.4	2.45/1
n-BuO (**1c**)	1.55	83.1	1.34/1

Table 2 Combined yields and individual yields of vanillin and isovanillin

R	Yield (%)[a]	Yield (%)[b]		Ratio (vanillin/isovanillin)
		Vanillin	Isovanillin	
n-Pr (**2a** + **3a**)	95.3	53.9	41.4	1.30/1
i-Pr (**2b** + **3b**)	96.0	68.4	27.6	2.48/1
n-Bu (**2c** + **3c**)	88.2	50.7	37.5	1.35/1

[a] Combined isolated yield of vanillin and isovanillin

[b] Individual isolated yield

Previously, the *i*-propyl group has properly served as a protecting group for hydroxy group of phenolic compounds, and its selective removal easily occurs under acidic conditions such as HBr–HOAc as well as Lewis acid [12, 15–17]. In the case of substrates **2c** and **3c** containing more difficult deblocking of *n*-butoxy group, we examined HBr–HOAc system, as well as Lewis acid $TiCl_4$ and $AlCl_3$, to remove the *n*-butyl group. The experimental results revealed that the pleasing aluminium trichloride is absolutely able to cleave *n*-butoxy group under ambient temperature with the methoxyl groups maintained intact. In the optimized reaction conditions, with 2.1 equiv. anhydrous aluminium trichloride for 18 h, the cleavage of the *n*-butoxy group for **2c** and **3c** brought about vanillin and isovanillin in 88.2 % combined yield. In contrast, the cleavage of the *n*-propoxy group for **2a** and **3a**, and *i*-propoxy group for **2b** and **3b** completely resulted in vanillin and isovanillin in more than 95 % combined yields needing only 5 h (Table 2). Furthermore, for the *i*-propoxy group-containing aromatic aldehydes **2b** and **3b**, 1.8 equiv. anhydrous aluminium trichloride is sufficient to remove the *i*-propyl groups. Consequently, the ease of removing the alkyl groups with anhydrous aluminium trichloride give a sequence of *i*-Pr > *n*-Pr > *n*-Bu. A few methods for de-*n*-propylation and de-*n*-butylation have been reported; however, either harsh reaction conditions or lower yields gave rise to poorer accessibility [18–21]. Distinctively, our procedure of dealkylation by anhydrous aluminium trichloride is a mild convenient and efficient process, as well as having outstanding selectivity for fully retaining the methyl group.

Conclusions

In conclusion, we have developed a novel method for concurrent synthesis of two significant fine chemicals, vanillin and isovanillin, by a nonregioselective

Vilsmeier–Haack formylation of *O*-alkyl guaiacols with *N*-methylformanilide/phosphorus oxychloride in good yields. By means of chemical nonregioselectivity, the methodology of simultaneous synthesis of two great organic compounds is a rewarding attempt in synthetic chemistry. In addition, compared to a sterically hindered *i*-propyl group containing the relatively active methenyl (CH) group, efficient adoption and selective removal of the inert *n*-propyl and *n*-butyl groups are of potential and special applications in the strategy of protecting groups.

Experimental

The NMR spectra were recorded on Bruker AV400 spectrometer at 400 and 100 MHz, for ^{1}H and ^{13}C, respectively, and the chemical shifts were expressed in δ ppm relative to tetramethylsilane as an internal standard. MS and HRMS were carried out on a Micromass GCTTM gas chromatograph-mass spectrometer and a QSTAR Pulsar I LC/TOF MS mass spectrometer, respectively. The melting points were recorded on open capillaries and are uncorrected. All solvents and reagents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) was performed on silica gel HF254 and TLC visualizations were performed with ultraviolet (UV) light.

General procedure for preparation of 1-alkoxy-2-methoxybenzene (**1**)

To ethanol (80 mL) were added guaiacol (6.2 g, 0.05 mol), potassium carbonate (13.8 g, 0.10 mol), alkyl bromide (0.10 mol), and potassium iodide (1.7 g, 0.01 mmol), and the mixture was heated to reflux. The progress of the reaction was monitored by TLC (typically within 10–24 h). After the reaction had finished, the mixture was filtered, concentrated, and passed through a short column of silica gel (eluent: dichloromethane) to get the 1-alkoxy-2-methoxybenzene (**1**) as a pale yellow liquid with 88.0–95.3 % yields.

*1-Methoxy-2-n-propoxybenzene (**1a**)*

7.9 g (95.3 %, 10 h); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.87–6.93 (m, 4H, Ar), 3.99 (t, $J = 6.8$ Hz, 2H, CH_2), 3.87 (s, 3H, CH_3), 1.88 (sext, $J = 7.2$ Hz, 2H, CH_2), 1.05 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 149.43, 148.57, 120.83, 120.81, 113.06, 111.82, 70.42, 55.94, 22.50, 10.45; MS-EI (*m/z*): 166.1 (M^+); HRMS (ESI): *m/z* ($M + Na^+$) calcd. for $C_{10}H_{14}O_2Na$: 189.0891; found: 189.0886.

*1-Methoxy-2-i-propoxybenzene (**1b**)*

7.3 g (88.0 %, 24 h); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.88–6.98 (m, 4H, Ar), 4.53 (heptet, $J = 6.0$ Hz, 1H, CH), 3.86 (s, 3H, CH_3), 1.37 (d, $J = 6.0$ Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 150.52, 147.35, 121.30, 120.79, 116.12, 112.14, 71.41, 55.92, 22.14 (2C); MS-EI (*m/z*): 166.1 (M^+); HRMS (ESI): *m/z* ($M + Na^+$) calcd. for $C_{10}H_{14}O_2Na$: 189.0891; found: 189.0886.

*1-n-Butoxy-2-methoxybenzene (**1c**)*

8.5 g (94.4 %, 15 h); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.96–6.85 (m, 4H, Ar), 4.03 (t, $J = 6.8$ Hz, 2H, CH_2), 3.87 (s, 3H, CH_3), 1.84 (quint, $J = 7.2$ Hz, 2H, CH_2), 1.51 (sext, $J = 7.2$ Hz, 2H, CH_2), 0.99 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 149.43, 148.61, 120.83, 120.78, 113.02, 111.81, 68.64, 55.95, 31.26, 19.23, 13.90; MS-EI (*m/z*): 180.1 (M^+); HRMS (ESI): *m/z* ($M + Na^+$) calcd. for $C_{11}H_{16}O_2Na$: 203.1048; found: 203.1050.

General procedure for preparation of 4-alkoxy-3-methoxybenzaldehyde (**2**) and 3-alkoxy-4-methoxybenzaldehyde (**3**)

Phosphorus oxychloride (9.2 g, 0.06 mol) was added dropwise to a stirred mixture of cold (ice bath) *N*-methylformanilide (8.1 g, 0.06 mol) and the compound **1** (0.04 mol). The mixture was heated at 115 °C for 1 h, and then at 100 °C for 18 h. After the reaction had finished, the mixture was cooled, and then basified with an aqueous solution of sodium hydroxide (2 mol/L, 100 mL) and extracted with dichloromethane (150 mL × 3). The separated organic phase was concentrated, and then distilled in vacuo to provide the mixture of **2** and **3** as yellow liquid with 81.8–84.4 %.

*3-Methoxy-4-n-propoxybenzaldehyde (**2a**) and 4-methoxy-3-n-propoxybenzaldehyde (**3a**)*

6.3 g (81.8 %); bp 123–126 °C/2 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$, **2a** and **3a**), δ (ppm): 9.82 (s, 2H, CHO), 7.46–7.40 (m, 2H, Ar), 7.39–7.37 (m, 2H, Ar), 6.96 (d, $J = 8.4$ Hz, 1H, Ar), 6.95 (d, $J = 8.0$ Hz, 1H, Ar), 4.05 (t, $J = 6.8$ Hz, 2H, CH_2), 4.02 (t, $J = 6.8$ Hz, 2H, CH_2), 3.93 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 1.95–1.80 (m, 4H, CH_2), 1.043 (t, $J = 7.6$ Hz, 3H, CH_3), 1.035 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, **2a** and **3a**), δ (ppm): 190.97, 190.91, 154.84, 154.18, 149.84, 149.13, 130.08, 129.87, 126.80, 126.59, 110.39, 110.61, 110.29, 109.27, 70.57, 70.49, 56.17, 56.03, 22.32, 22.27, 10.39, 10.37; MS-EI (*m/z*): 194.1 (M^+); HRMS (ESI): *m/z* ($M + H^+$) calcd. for $C_{11}H_{15}O_3$: 195.1021; found: 195.1019.

*3-Methoxy-4-i-propoxybenzaldehyde (**2b**) and 4-methoxy-3-i-propoxybenzaldehyde (**3b**)*

6.5 g (84.4 %); bp 115–119 °C/2 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$, **2b** and **3b**), δ (ppm): 9.80 (s, 2H, CHO), 7.43–7.35 (m, 4H, Ar), 6.94 (d, $J = 8.0$ Hz, 2H, Ar), 4.70–4.55 (m, 2H, CH), 3.90 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 1.39 (d, $J = 6.4$ Hz, 6H, CH_3), 1.36 (d, $J = 6.4$ Hz, 6H, CH_3); ^{13}C NMR (100 MHz, CDCl3, **2b** and **3b**), δ (ppm): 190.98, 190.88, 155.61, 153.09, 150.33, 147.82, 130.00, 129.70, 126.63, 126.50, 112.82, 112.57, 110.90, 109.53, 71.30, 71.27, 56.13, 55.99, 21.89 (2C), 21.85 (2C); MS-EI (*m/z*): 194.1 (M^+); HRMS (ESI): *m/z* ($M + H^+$) calcd. for $C_{11}H_{15}O_3$: 195.1021; found: 195.1013.

*4-n-Butoxy-3-methoxybenzaldehyde (**2c**) and 3-n-butoxy-4-methoxybenzaldehyde (**3c**)*

6.8 g (83.1 %); bp 140–144 °C/2 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$, **2c** and **3c**), δ (ppm): 9.80 (s, 2H, CHO), 7.42–7.37 (m, 2H, Ar), 7.364 (s, 1H, Ar), 7.360 (s, 1H, Ar), 6.931 (d, J = 8.4 Hz, 1H, Ar), 6.927 (d, J = 8.4 Hz, 1H, Ar), 4.06 (t, J = 6.8 Hz, 2H, CH_2), 4.04 (t, J = 6.8 Hz, 2H, CH_2), 3.90 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 1.86–1.76 (m, 4H, CH_2), 1.54–1.40 (m, 4H, CH_2), 0.949 (t, J = 7.6 Hz, 3H, CH_3), 0.945 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, **2c** and **3c**), δ (ppm): 190.95, 190.88, 154.82, 154.19, 149.82, 149.14, 130.05, 129.83, 126.78, 126.57, 111.35, 110.58, 110.20, 109.23, 68.82, 68.70, 56.13, 55.99, 31.03, 30.94, 19.16, 19.13, 13.82, 13.80; MS-EI (*m/z*): 208.1 (M^+); HRMS (ESI): *m/z* ($M + H^+$) calcd. for $C_{12}H_{17}O_3$: 209.1178; found: 209.1178.

General procedure for preparation of vanillin [22] and isovanillin [5]

A solution of the mixture of **2** and **3** (10 mmol) in dichloromethane (30 mL) was stirred at room temperature for 10 min. To the mixture was added in one portion anhydrous aluminium trichloride (21 mmol to the mixture of **2a** and **3a** as well as the mixture of **2c** and **3c**, 18 mmol to the mixture of **2b** and **3b**). The resulting solution was stirred at room temperature for a corresponding time (5 h for the mixture of **2a** and **3a** as well as the mixture of **2b** and **3b**, and 18 h for the mixture of **2c** and **3c**). The reaction solution was quenched with aqueous ammonium chloride (2 mol/L, 50 mL) and extracted with dichloromethane (50 mL ×3). The separated organic phase was washed with saturated brines (60 mL ×2) and concentrated to provide the crude products, which were isolated by column chromatography (eluent: petroleum ether/ethyl acetate = 10/1) to yield vanillin and isovanillin.

Vanillin from **2a**: 0.82 g (53.9 %), off-white solid; mp 80–82 °C ([22]: 81–84 °C); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 9.81 (s, 1H, CHO), 7.44–7.39 (m, 2H, Ar), 7.03 (d, J = 8.4 Hz, 1H, Ar), 6.43 (s, 1H, OH), 3.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 191.02, 151.78, 147.21, 129.83, 127.58, 114.45, 108.83, 56.12; MS-EI (*m/z*): 152.0 (M^+); HRMS (ESI): *m/z* ($M + H^+$) calcd. for $C_8H_9O_3$: 153.0552; found: 153.0559.

Isovanillin from **3a**: 0.63 g (41.4 % yield), off-white solid; mp: 115–117 °C ([23: 113–116 °C); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 9.82 (s, 1H, CHO), 7.45–7.38 (m, 2H, Ar), 6.95 (d, J = 8.0 Hz, 1H, Ar), 5.97 (s, 1H, OH), 3.96 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 191.12, 151.94, 146.21, 130.64, 124.63, 114.09, 110.26, 56.20; MS-EI (*m/z*): 152.1 (M^+) HRMS (ESI): *m/z* ($M + H^+$) calcd. for $C_8H_9O_3$: 153.0552; found: 153.0553.

Vanillin from **2b**: 1.04 g (68.4 %).
Isovanillin from **3b**: 0.42 g (27.6 %).
Vanillin from **2c**: 0.77 g (50.7 %).
Isovanillin from **3c**: 0.57 g (37.5 %).

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References

1. H.R. Bjørsvik, L. Liguori, F. Minisci, Org. Process Res. Dev. **4**, 534 (2000)
2. K. Li, J.W. Frost, J. Am. Chem. Soc. **120**, 10545 (1998)
3. H.R. Bjørsvik, F. Minisci, Org. Process Res. Dev. **3**, 330 (1999)
4. X. Wang, T. Ju, X. Li, X. Cao, Synlett. **21**, 2947 (2010)
5. K. Bao, A. Fan, Y. Dai, L. Zhang, W. Zhang, M. Cheng, X. Yao, Org. Biomol. Chem. **7**, 5084 (2009)
6. S. Umemura, N. Takamitsu, T. Enomiya, H. Shiraishi, T. Nakamura, U.S. Patent 4,165,341 (July 28, 1979)
7. K. Nobuyuki, EP 758639 (February 19, 1997)
8. C. Maliverney, U.S. Patent 5,786,516 (July 28, 1998)
9. L.N. Ferguson, Chem. Rev. **38**, 227 (1946)
10. J. Szilagyi, J. Halmos, S. Szabo, F. Szileczky, J. Mezei, T. Szabolcsi, G. Kortvelyessi, J. Nyitrai, I. Miskolczi, K. Szatmari, HU 55741 (June 28, 1991)
11. J.A. Mitchell, J. Chem. Soc. 1792 (1937)
12. R.J. Bushby, Z. Lu, Synthesis **33**, 763 (2001)
13. R.W. Taft, in *Steric Effects in Organic Chemistry*, ed. by M.S. Newman (Wiley, New York, 1956)
14. C. Hansch, A. Leo, D. Hoekman, *Exploring QSAR: Volume 2: Hydrophobic Electronic and Steric Constants* (American Chemical Society, Washington, DC, 1995)
15. J.P. Gillespie, L.G. Amoros, F.R. Stermitz, J. Org. Chem. **39**, 3239 (1974)
16. T.W. Greene, P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edn. (Wiley, New York, 1999)
17. M.G. Banwell, B.L. Flynn, S.G. Stewart, J. Org. Chem. **63**, 9139 (1998)
18. L. Tong, B.J. Lavey, B.B. Shankar, S.H. Kim, W. Yu, J.A. Zlowski, K.C. Michael, L. Chen, G. Zhou, WO 054278 (May 14, 2010)
19. A. Palmeira, M.H. Vasconcelos, A. Paiva, M.X. Fernandes, M. Pinto, E. Sousa, Biochem. Pharmacol. **83**, 57 (2012)
20. F. Rombouts, D. Franken, M. Braeken, C. Zavattaro, J. Chen, A.A. Trabanco, Tetrahedron Lett. **51**, 4815 (2010)
21. A. Vass, J. Dudas, F. Haasz, P. Jekkel, WO 061066 (June 15, 2006)
22. P. Gogoi, P. Hazarika, D. Konwar, J. Org. Chem. **70**, 1934 (2005)
23. M.L. Scarpati, A. Bianco, L. Mascitelli, P. Passacantilli, Synth. Commun. **20**, 2565 (1990)