Asian Journal of Chemistry; Vol. 30, No. 1 (2018), 85-88

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.20912

Green and Simple Synthesis of *p*-Anisic acid and Other Analogs from Methyl Paraben

SENTHIL PERIYASAMY and SELVARAJ SUBBIAH*

Post Graduate and Research Department of Chemistry, Sri Paramakalyani College, Alwarkurichi-627 412, India

*Corresponding author: E-mail: drselvarajspkc@gmail.com

Received: 6 July 2017; *Accepted*: 20 September 2017; *Published online*: 30 November 2017; AJC-18656

Synthesis of *p*-anisic acid from commercially available methyl paraben was obtained in good yield and performed the each steps in shorter duration is reported. The E-factor was evaluated for each step was 3.0 and 2.30 respectively without transition metals content in the waste disposal. The solvents used in each steps were completely recovered and recycled in the consecutive batches. This methodology was applied to the synthesis of *p*-ethoxy benzoic acid and *p*-propyloxy benzoic acid and the other derivatives from methyl paraben obtained in good yield.

Keywords: Methyl paraben, *p*-Anisic acid, E-factor, Transition metals, *p*-Ethoxy benzoic acid, *p*-Propyloxy benzoic acid.

INTRODUCTION

p-Anisic acid is the key raw material in many pharmaceutical applications. It has a significant role in food and cosmetics industries [1]. Several synthetic methodologies are reported in the literature from alcohols, aldehydes, ketones and nitriles to prepare the corresponding carboxylic acids. Synthetic methodology involves the preparation from (A) *p*-methoxy benzyl alcohol by (i) insertion of oxygen atom of nitrous oxide into rhodium complex [2] (ii) sodium hypochlorite oxidation in the presence of catalytic amount of oxoammonium salts [3] (iii) photo oxidation using N-bromosuccinimide [4] (iv) dehydrogenation using NHC-ruthenium complex [5] (B) *p*-methoxybenzaldehyde (v) oxidation using 70 % *t*-butyl hydrogen peroxide in the presence of catalytic amount of 10 mol % of Mohr's salt [6] (vi) sodium chlorite-35 % hydrogen peroxide oxidation using oxygen scavengers [7] (vii) diphenyl-diselenide oxidation with stoichiometric hydrogen peroxide [8] (III) *p*-methoxyacetophenone (viii) pH controlled oxidation of *p*-methoxyacetophenone by sodium hypochlorite [9,10] (ix) hydrogen peroxide oxidation in the presence of catalyst in ionic liquid [11] (x) in presence of the trifluoro acetic acid by oxone [12] (xi) cobalt carbonyl catalyzed carbonylation of 4-bromo anisole [13,14] (xii) carboxylation of 4-bromoanisole by four membered ring disilane [15] (xiii) oxidation of 4-methoxy benzyl amine [16] (xiv) debenzylation of benzyl-4-methoxy benzoate in the presence of silica supported sodium hydrogen sulphate [17] and (xv) oxidation of *p*-methoxy toluene in the presence of a mixture of catalyst [18].

The reported processes have many drawbacks like problems in disposal of heavy metals in the effluent, use of costly reagents, low yields and tedious procedure. Thus, herein, the cost effective methodology to decrease the operational cost and minimum effluents in the disposal without using transition metals and the aqueous waste were disposed followed by neutralization to pH 7-8 is presented. This robust process was evaluated with green matrics such as E-factor, atom economy, atom efficiency, carbon efficiency and reaction mass efficiency. Some of the other useful intermediates which were identified potentially biological active molecules also synthesized from methyl paraben by using this process.

EXPERIMENTAL

All reagents purchased from commercial sources were used as received. All melting points taken from open capillary tube and are uncorrected. The ^{1}H and ^{13}C NMR spectra are referenced to the residual.

Solvents signals (7.26 ppm and 2.50 ppm for ^{1}H NMR in $CDCl_3$ and DMSO-d_6, 77.0 ppm and 39.0 ppm for ^{13}C NMR in $CDCl_3$ and DMSO-d_6) are reported. All the reactions were carried out in oven-dried glassware and were mechanically stirred. Kilo lab trials were optimized using 100 L stainless steel and glass line reactor.

Methyl-4-methoxy benzoate (2): To the stirred solution of methyl paraben (0.500 Kg, 3.28 mol) was treated with dimethyl sulphate (0.622 Kg, 4.92 mol) in the presence of potassium carbonate (0.907 Kg, 6.57 mol) in 2-butanone (3500 mL) for 2.0 h at 78-80 °C. Completion of the reaction was confirmed by TLC and GC. Added potable water (2000 mL) and stirred for 30 min and allowed the layers for separation. Separated the organic layer and recovered 2-butanone (3325 mL)

recycled for the next consecutive three batches and isolated (2).Yield: 0.542 Kg, 99.26 %.

IR (neat, cm^{-1}): 1705.62, 1603.86, 1508.90, 1317.76, 1282.33, 1250.73, 1166.55, 1104.11. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.02-7.97 (m, 2H, ArH), 6.94-6.89 (m, 2H, ArH) 3.88 (s, 3H, O$\underline{CH_3}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 166.87, 163.32, 131.59, 131.19, 122.59, 113.59, 55.41, 51.86.

Methyl-4-ethoxy benzoate (3): To the stirred solution of methyl paraben (0.100 Kg, 0.657 mol) was treated with diethyl sulphate (0.152 Kg, 0.98 mol) in the presence of potassium carbonate (0.181 Kg, 1.31 mol) in 2-butanone (700 mL). Followed the procedure as mentioned in compound (2) and isolated the product (3).Yield: 0.118 Kg, 99.64 %.

IR (neat, cm^{-1}): 1712.76, 1605.23, 1510.51, 1314.17, 1277.93, 1248.85, 1166.72, 1101.82. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.00-7.95 (m, 2H, ArH), 6.92-6.87 (m, 2H, ArH) 4.07 (q, 2H, O$\underline{CH_2}$, J = 6.9 Hz), 3.87 (s, 3H, O$\underline{CH_3}$), 1.41 (t, 3H, $\underline{CH_3}$, J = 4.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 166.90, 162.75, 131.96, 131.57, 131.17, 122.71, 122.36, 114.02, 63.66, 60.59, 51.82, 29.70, 14.67.

Methyl-4-propoxy benzoate (4): To the stirred solution of methyl paraben (0.200 Kg, 1.31 mol) was treated with 1-bromopropane (0.194 Kg, 1.57 mol) in the presence of K_2CO_3 (0.362 Kg, 2.62 mol) in 2-butanone (1400 mL). Followed the procedure as mentioned in compound **2** and isolated the product (4). Yield: 0.246 Kg, 96.52 %.

IR (neat, cm^{-1}): 1713.00, 1603.95, 1510.33, 1434.11, 1248.30, 1165.47, 1101.66, 1012.26, 975.60. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.00-7.95 (m, 1H,ArH), 6.92-6.87 (m, 1H, ArH), 3.95 (t, 2H, O$\underline{CH_2}$, J = 6.6 Hz), 3.87 (s, 3H, O$\underline{CH_3}$), 1.88-1.76 (m, 2H, CH_3-$\underline{CH_2}$-OCH_2), 1.06 (s, 3H, $\underline{CH_3}$, J = 4.8 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 166.90, 162.94, 131.55, 131.15, 122.30, 113.62, 69.63, 51.80, 22.45, 10.45.

Methyl 4-[(4-cyanobenzyl)oxy]benzoate (5): To the stirred solution of methyl paraben (0.200 Kg, 1.31 mol) was treated with 4-cyanobenzyl bromide (0.309 Kg, 1.57 mol) in the presence of potassium carbonate (0.362 Kg, 2.62 mol) in 2-butanone (1400 mL). Followed the procedure as mentioned in compound (2) and isolated the product (5). Yield: 0.342 Kg, 97.34 %. White crystalline solid. m.p.: 148-150 °C.

IR (neat, cm^{-1}): 1708.77, 1607.85, 1513.09, 1434.28, 1319.80, 1260.35, 1165.85, 1107.07. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.03-7.98 (m, 2H, ArH), 7.69 (d, 2H, ArH, J = 8.1 Hz), 7.55 (d, 2H, ArH, J = 8.1 Hz), 7.00-6.95 (m, 2H, ArH), 5.18 (s, 2H, O$\underline{CH_2}$), 3.89 (s, 3H, O$\underline{CH_3}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 166.65, 161.79, 141.69, 132.50, 131.73, 127.58, 123.42, 118.59, 114.39, 111.98, 68.92, 51.98.

Methyl4-[(2'-cyanobiphenyl-4-yl)methoxy]benzoate (6): To the stirred solution of methyl paraben (0.200 Kg, 1.31 mol) was treated with 4'-bromomethyl-2-cyano biphenyl (0.429 Kg, 1.57 mol) in the presence of potassium carbonate (0.362 Kg, 2.62 mol) in 2-butanone (1400 mL). Followed the procedure as mentioned in compound (2) and isolated the product (6). Yield: 0.422 Kg, 93.50 %. White solid. m.p.: 108-112.5 °C.

IR (neat, cm^{-1}): 1718.24, 1609.60, 1510.99, 1484.86, 1375.75, 1287.04, 1257.12, 1223.30, 1166.71, 1111.78. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.01 (dd, 2H, ArH, J = 6.9 Hz, 1.8 Hz), 7.78 (d, 1H, ArH, J = 7.8 Hz), 7.69-7.43 (m, 7H, ArH), 7.02 (d, 2H, ArH, J = 9 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 166.82, 162.36, 144.96, 138.03, 136.88, 133.81, 132.91, 131.69, 130.05, 129.11, 127.79, 127.73, 123.00, 118.68, 114.46, 111.27, 69.64, 51.92.

General procedure for hydrolysis: To the stirred solution of the ester was prepared above treated with sodium hydroxide (2.0 eq) in methanol at 60-65 °C for 3 h. Acidified the reaction mixture with hydrochloric acid and isolated the corresponding product in good yield and methanol was recovered.

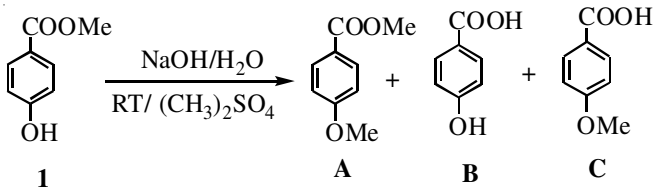
4-Methoxy benzoic acid (7): Yield: 0.540 Kg, 99.67 %. White solid. m.p.: 183-184.5 °C. IR (neat, cm^{-1}): 1678.79, 1600.24, 1573.84, 1513.92, 1425.40, 1297.25, 1259.13, 1164.26, 1128.89, 1023.86. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.91-7.868 (m, 2H, ArH), 7.03-6.98 (m, 2H, ArH), 3.81(s, 3H, O$\underline{CH_3}$). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C166.97, 162.81, 131.70, 131.32, 130.93, 122.81, 113.77, 55.37.

4-Ethoxy benzoic acid (8): Yield: 0.116 Kg, 98.40 %. White solid. m.p.: 197-200 °C. IR (neat, cm^{-1}): 1673.00, 1606.20, 1577.07, 1299.52, 1259.72, 1172.95, 1114.27, 1042.41, 921.42. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.89-7.85 (m, 2H, ArH), 7.00-6.97 (m, 2H, ArH), 4.08 (q, 2H, O$\underline{CH_2}$, J = 6.9 Hz), 1.33 (t, 3H, $\underline{CH_3}$, J = 6.9 Hz). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 166.91, 162.12, 131.32, 122.60, 114.14, 63.39, 14.45.

4-Propoxy benzoic acid (9): Yield: 0.243 Kg, 98.90 %. White solid. m.p.: 144-145.8 °C. IR (neat, cm^{-1}): 1712.91, 1604.02, 1510.38, 1434.16, 1248.53, 1165.57, 1101.89, 1044.79, 1012.33, 975.66. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.89-7.85 (m, 2H, ArH), 7.00 (d, 2H, ArH, J = 7.2 Hz), 3.98 (q, 2H, OCH_2-$\underline{CH_2}$-CH_3, J = 6.6 Hz), 1.79-1.67 (m, 2H,-OCH_2-$\underline{CH_2}$-CH_3), 0.970 (t, 3H,-OCH_2-CH_2-$\underline{CH_3}$, J = 7.2 Hz). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 166.92, 162.28, 131.32, 122.61, 114.17, 69.18, 21.86, 10.28.

RESULTS AND DISCUSSION

We initially treated methyl paraben in water in the presence of sodium hydroxide (2.0 eq) at room temperature afforded the mixture of products (**Scheme-I**). Though the reaction was stirred for 24 h, was obtained 40 % unreacted methyl paraben (B) and 60 % of the desired corresponding product (A) which is confirmed by gas chromatography. When treated with sodium bicarbonate, O-alkylation when compared to potassium carbonate is too slow and found 15-20 % unreacted methyl paraben by gas chromatography. When it was stirred in 2-butanone with potassium carbonate and dimethyl sulphate, it afforded methyl 4-methoxy benzoate in 99.13 % yield which upon hydrolysis gave *p*-anisic acid in 99.67 % yield. 95 % of 2-butanone and methanol were recovered after the process and recycled for the next three consecutive batches.

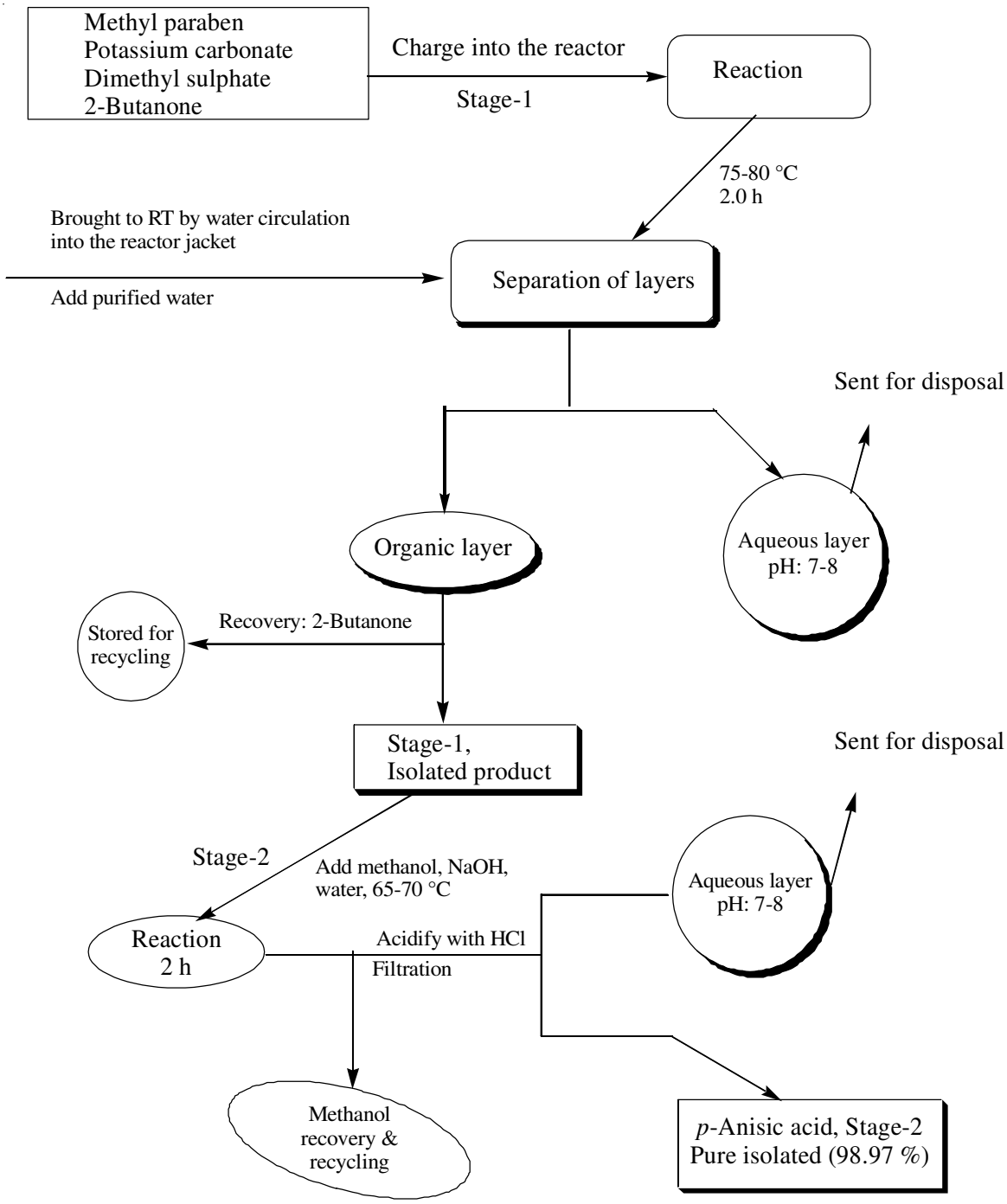


1 **A** **B** **C**

Scheme-I

As like, the process optimization and the yield obtained for *p*-anisic acid, we became interested into synthesize *p*-ethoxy and *p*-propyloxy benzoic acids. Treated the methyl paraben with diethyl sulphate and obtained methyl 4-ethoxy benzoate in 99.46 % yield which upon hydrolysis afforded 98.40 % yield of *p*-ethoxy benzoic acid. To synthesize, *p*-propyloxy benzoic acid, we tried to reduce the cost of di *n*-propyl sulphate as we received the quote from various vendors. But the cost was not suitable for this viable process and chosen the commercially cheaper *n*-propyl bromide when compared to di *n*-propyl sulphate and obtained methyl 4-propoxy benzoate in 96.52 % yield which upon hydrolysis afforded 98.90 % yield and *p*-propyloxy benzoic acid. Similarly, we synthesized two important skeletons for present research, using methyl paraben treated with 4-cyanobenzyl bromide and 4'-bromomethyl-2-cyanobiphenyl afforded methyl 4-[(4-cyanobenzyl)oxy]benzoate and methyl 4-[(2'-cyanobiphenyl-4-yl)methoxy]benzoate, respectively above 90 % yield. The isolated product stage-1 (O-alkylation) and stage-2 (hydrolysis) of three recovered batches whose quality met with the pharmacopeia standard as per the ICH guidelines and the yields were obtained with consistency.

The process flow chart (**Scheme-II**) explained the kilo lab process optimization on 5 Kg scale. The first step (O-alkylation) was carried out in 100 L SSR (stainless steel reactor) and gave the product (5.41 Kg, 99.08 %) as obtained in lab trial



Scheme-II: Process flow chart for the synthesis of *p*-anisic acid

batches which was hydrolyzed in 100 L SSR and charcoalized the reaction mass with activated charcoal to get decolourized then the reaction mixture passed through filter line (Sparkler) to get clear solution and it was passed into 100 L GLR (glass line reactor). Acidified with conc. HCl and isolated pure product obtained in 99.39 % yield (4.91 Kg). Solvents were recovered and recycled further. The aqueous waste generated in each stage were neutralized and discarded.

E-factor is one of the key roles in controlling the effluent waste and we have calculated and evaluated the E-factor [19,20] for the two stages. The total waste per Kg product generated 1.6 Kg (Stage-1) and 1.13 Kg (Stage-2) without heavy metals content and obtained the consistency with the three recovered batches and the corresponding E-factor 3.0 (Stage-1) and 2.30 (Stage-2) respectively. According to Green Chemistry principles (U.S. Environmental protection agency), the E-factor for the pharmaceuticals between 25-100 [21]. This optimized process was within the limit and we have obtained this consistency below the value of E-factor 5.

Conclusion

This robust process is cost effective, transition metal free and all the raw materials are commercially available in low-cost price, hence it is industrially viable, sustainable process and suitable for the bulk scale up. Since the heavy metal content should be less than 10-20 ppm according to ICH guidelines and this process has no heavy metal content and there is no hazardous waste in the effluent. The consistency was achieved for three recovered and kilo lab batches for the E-factor.

ACKNOWLEDGEMENTS

The authors are grateful to Mr. Shailesh D. Siroya, Managing Director, Bal Pharma Ltd., Bangalore, India for providing the analytical support for NMR and IR studies.

REFERENCES

1. U. Straetmans, J. Janichen, W. Petersen, M. Kinder, C. Johnson and G. Reynolds, Concentrated, Aqueous Solutions of *p*-Methoxybenzoic acid for use in Cosmetic and Dermatologic Formulations US Patent 20060229291A1 (2006).
2. T.L. Gianetti, S.P. Annen, G. Santiso-Quinones, M. Reiher, M. Driess and H. Grützmacher, *Angew. Chem. Int. Ed.*, **55**, 1854 (2016); https://doi.org/10.1002/anie.201509288.
3. P.L. Anelli, C. Biffi, F. Montanari and S. Quici, *J. Org. Chem.*, **52**, 2559 (1987); https://doi.org/10.1021/jo00388a038.
4. A. Kioytokuwabara and I. Itoh, *Synthesis*, 1949 (2006); https://doi.org/10.1055/s-2006-942374.
5. J. Malineni, H. Keul and M. Möller, *Dalton Trans.*, **44**, 17409 (2015); https://doi.org/10.1039/C5DT01358E.
6. D. Chakraborty, C. Majumder and P. Malik, *Appl. Organomet. Chem.*, **25**, 487 (2011); https://doi.org/10.1002/aoc.1787.
7. E. Dalcanale and F. Montanari, *J. Org. Chem.*, **51**, 567 (1986); https://doi.org/10.1021/jo00354a037.
8. L. sancineto, C. Tidei, L. Bagnoli, F. Marini, E. Lenardão and C. Santi, *Molecules*, **20**, 10496 (2015); https://doi.org/10.3390/molecules200610496.
9. C.E. Ballard, *J. Chem. Educ.*, **87**, 190 (2010); https://doi.org/10.1021/ed800054s.
10. P. Sathyanarayana, O. Ravi, P.R. Muktapuram and S.R. Bathula, *J. Org. Biomol. Chem.*, **37**, 9681 (2015); https://doi.org/10.1039/C5OB01569C.
11. Y.-L. Hu, D.-J. Li and D.-S. Li, *RSC Adv.*, **5**, 24936 (2015); https://doi.org/10.1039/C5RA02234G.
12. K.A. Aravindakumar, V. Venkateswarlu, R. Vishwakarma and S. Sawant, *Synthesis*, **47**, 3161 (2015); https://doi.org/10.1055/s-0034-1381026.
13. J.J. Brunet, C. Sidot and P. Caubere, *Tetrahedron Lett.*, **22**, 1013 (1981); https://doi.org/10.1016/S0040-4039(01)82853-7.
14. M. Markovic, P. Lopatka, P. Koós and T. Gracza, *Org. Lett.*, **17**, 5618 (2015); https://doi.org/10.1021/acs.orglett.5b02840.
15. T. mita, K. Suga, K. Sato and Y. Sato, *Org. Lett.*, **17**, 5276 (2015); https://doi.org/10.1021/acs.orglett.5b02645.
16. R. Naik and M.A. Pasha, *Synth. Commun.*, **36**, 165 (2006); https://doi.org/10.1080/00397910500334165.
17. Y.W. Hu, L. Zuo, D.Y. Ye and W.H. Duan, *Chin. Chem. Lett.*, **20**, 1157 (2009); https://doi.org/10.1016/j.cclet.2009.04.028.
18. K.A. Fjare, Process for Preparation of *p*-Hydroxybenzoic Acid from *p*-Methoxytoluene, US Patent 4740614 (1988).
19. D.J.C. Constable, A.D. Curzons and V.L. Cunningham, *Green Chem.*, **4**, 521 (2002); https://doi.org/10.1039/B206169B.
20. R.A. Sheldon, *Chem. Ind.*, 903 (1992).
21. P.T. Anastas and J.C. Warner, Green Chemistry: Theory and Practice, Oxford University Press (2000).