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A Facile Synthesis of 3-(Chloromethyl)-2-methyl-1,1′-biphenyl

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3-(Chloromethyl)-2-methyl-1,1′-biphenyl is a key intermediate for the preparation of bifenthrin, an insecticide which belongs to pyrethroid. The traditional synthetic process of 3-(chloromethyl)-2-methyl-1,1′-biphenyl is complicated and involves high-toxic and high-risk reagents such as thionyl chloride, lithium aluminum hydride and methyl iodide, which causes significant environmental problems and safety issues. Herein, a facile and efficient synthesis process of 3-(chloromethyl)-2- methyl-1,1′-biphenyl was developed. The synthetic process is shortened from 6 steps to only 4 steps and avoids the use of high-toxic and high-risk reagents. Moreover, 3-(chloromethyl)-2-methyl-1,1′-biphenyl can be obtained by simple purification process in high yield (73.9 %). Compared with the traditional synthetic process, the synthetic process of 3-(chloromethyl)-2-methyl-1,1′-biphenyl reported here is more environmental friendly and efficient.

Keywords: Bifenthrin, Intermediate, Biphenyl, Bromination, Amination

INTRODUCTION

3-(Chloromethyl)-2-methyl-1,1′-biphenyl is a key intermediate for the preparation of bifenthrin (Fig. 1), a pyrethroid insecticide used primarily against the red imported fire ant by influencing its nervous system [1-3]. The traditional synthetic process of 3-(chloromethyl)-2-methyl-1,1′-biphenyl consists of six steps (**Scheme-I**) [4] *viz.* (a) (1,1′-biphenyl)-2-carboxylic acid was chlorinated with thionyl chloride in the presence of pyridine to produce (1,1′-biphenyl)-2-carbonyl chloride; (b) (1,1′-biphenyl]-2-carbonyl chloride was reacted with N,N-dimethylformamide to produce N,N-dimethyl-(1,1′-biphenyl)-2-carboxamide; (c) N,N-dimethyl-(1,1′-biphenyl)-2-carboxamide was reduced by lithium aluminum hydride to produce N,N-dimethyl-(1,1′-biphenyl)-2-methanamine; (d) N,N-dimethyl-(1,1′-biphenyl)-2-methanamine was reacted with methyl iodide to obtain N,N,N-trimethyl-(1,1′-biphenyl)-2-methanaminium iodide; (e) N,N,N-trimethyl-(1,1′-biphenyl)-2-methanaminium iodide was converted to N,N-dimethyl-2-methyl-(1,1′-biphenyl)-3-methanamine in the presence sodium amide and liquid NH_3 by Sommelet-Hauser rearrangement; and finally (f) N,N-dimethyl-2-methyl-(1,1′-biphenyl)-3-methanamine was chlorinated with ethyl chloroformate to get the target compound 3-(chloromethyl)-2-methyl-1,1′-biphenyl. The whole synthetic process is complicated, which makes it difficult to control the quality of the synthesized product. The synthetic process involves high-toxic and high-risk reagents such as thionyl chloride, lithium aluminum hydride and methyl iodide, causing considerable environmental and safety problems. For example, use of thionyl chloride in the first step can produce highly corrosive hydrogen chloride, the use of lithium aluminum hydride in the third step can produce explosive gas hydrogen [5] and methyl iodide as a methylation reagent may have carcinogenic toxicity and neurotoxicity [6].

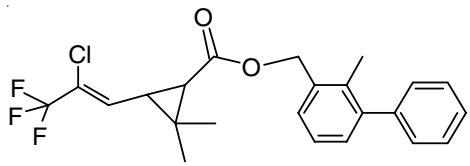

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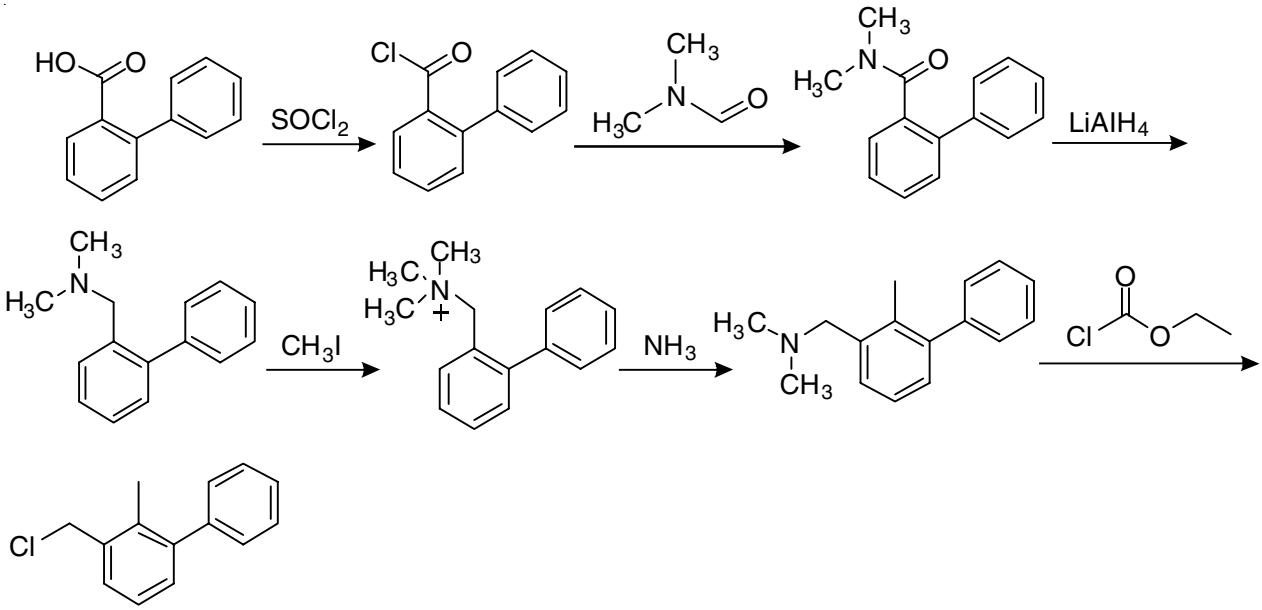
Fig. 1. Structure of bifenthrin

To overcome the deficiencies of the traditional synthetic process, a facile and clean synthetic process of 3-(chloromethyl)-2-methyl-1,1′-biphenyl is developed by using 2-methyl-1,1′-biphenyl as the starting material. The synthetic process is shortened to four steps and avoids the use of high-toxic and



Scheme-I: Traditional synthetic process of 3-(chloromethyl)-2-methyl-1,1'-biphenyl from [1,1'-biphenyl]-2-carboxylic acid

high-risk reagents. Moreover, 3-(chloromethyl)-2-methyl-1,1′-biphenyl can be obtained by simple purification process in high overall yield.

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers and used without further purification. The melting points were determined on a XT34 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. ^{1}H NMR spectra were recorded on Mercuryplus 300 MHz spectrometer. Chemical shifts (δ) were given in parts per million (ppm) relative to tetramethylsilane. Thin-layer chromatography (TLC) and column chromatography were performed on silica gel GF_{254} and silica gel H60, respectively. The purity of synthesized compounds was determined by high performance liquid chromatography (HPLC, 1260 Infinity, Agilent).

Synthesis of 2-(bromomethyl)-1,1′-biphenyl (3): Briefly, 2-methyl-1,1′-biphenyl (13.9 g, 83 mmol), N-bromosuccinimide (NBS,19.6 g, 110 mmol), and *tert*-butyl hydroperoxide (TBHP, 1.8 g, 20 mmol) were dissolved in cyclohexane (80 mL). Then, above mixture was heated to 42 ºC and maintained at 42-45 ºC for 2 h. The reaction mixture was cooled to room temperature and the formed succinic imide was removed by filtration. The filtrate was evaporated under vacuum to yield compound **3** as light yellow oily liquid (18.7 g, 91.2 % in yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.45 (m, 9 H, ArH), 4.87 (s, 2H, CH_2).

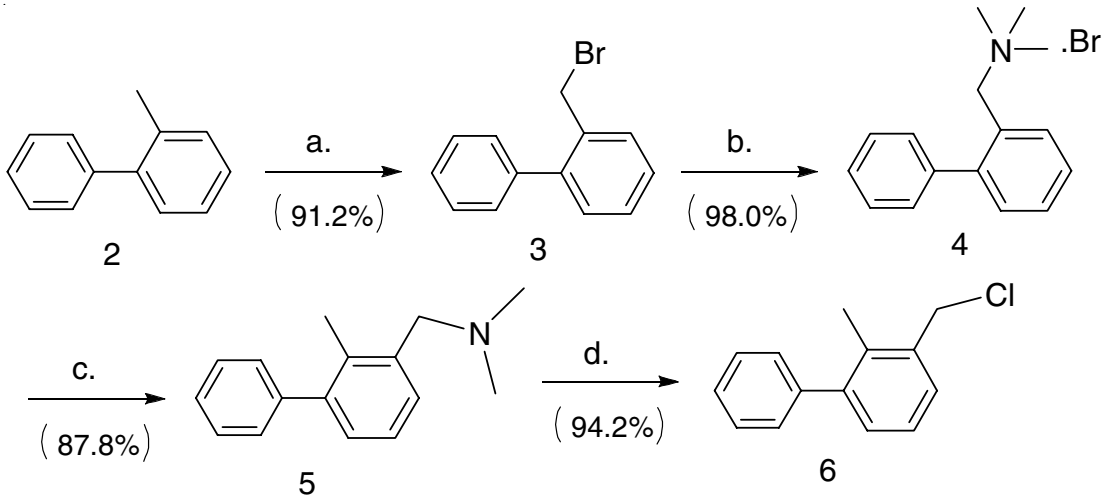
Synthesis of N,N,N-trimethyl-[1,1′-biphenyl]-2-methanaminium bromide (4): Briefly, 2-(bromomethyl)-1,1′-biphenyl (16.8 g, 67.9 mmol) and trimethylamine (4.42 g, 74.7 mmol) were dissolved in ethyl acetate (60 mL) and the resulting mixture was stirred at 32 ºC for 3 h. Then, the reaction mixture was cooled to room temperature and evaporated under vacuum to give compound **4** as white solid (21.5 g, 98.0 % in yield). m.p. 221.5-223.7 ºC (lit. [7], m.p. 220-225 ºC). ^{1}H NMR (300 MHz, D_2O): δ (ppm) 7.35 (m, 9 H, ArH), 4.51 (br s, 2H, CH_2), 2.65 (br s, 9H, CH_3).

Synthesis of N,N-dimethyl-2-methyl-[1,1'-biphenyl]-3-methanamine (5): Briefly, N,N,N-trimethyl-(1,1′-biphenyl)-2-methanaminium bromide (23 g, 75 mmol) and sodium amide (5.7 g, 146 mmol) were slowly added to liquid NH_3 (80 mL) under -50 ºC and the resulting mixture was stirred at -50 ºC for 4 h. The excess of sodium amide was neutralized by the addition of an aqueous solution of ammonium chloride. Afterwards, the reaction mixture was extracted with ethyl acetate (250 mL × 2). The extracts were combined and washed with brine, dried over anhydrous sodium sulfate and evaporated under vacuum to get compound **5** as light grey oily liquid (14.9 g, 87.8 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.35 (m, 8 H, ArH), 3.49 (s, 2H, CH_2), 2.34 (s, 6H, CH_3), 2.30 (s, 3H, CH_3).

Synthesis of 3-(chloromethyl)-2-methyl-1,1′-biphenyl (6): Briefly, N,N-dimethyl-2-methyl-(1,1′-biphenyl]-3-methanamine (20.7 g, 91.7 mmol) was dissolved in cyclohexane (80 mL) and heated to 80 ºC. To the solution, ethyl chloroformate (14.9 g, 137.8 mmol) was slowly added under stirring and the resulting mixture was stirred at 80 ºC for 3 h. The reaction mixture was cooled to room temperature and filtrated. The filtrate was evaporated under vacuum to give compound **6** as white solid (18.7 g, 94.2 %). m.p. 53.2-56.3 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.43 (m, 8 H, ArH), 4.96 (m, 2H, CH_2), 2.25 (m, 3H, CH_3).

RESULTS AND DISCUSSION

3-(Chloromethyl)-2-methyl-1,1′-biphenyl was synthesized from 2-methyl-1,1′- biphenyl through four steps (**Scheme-II**): (a) 2-methyl-1,1′-biphenyl was brominated with NBS in the presence of TBHP to produce 2-(bromomethyl)-1,1′-biphenyl [8,9]; (b) 2-(bromomethyl)-1,1′-biphenyl was reacted with trimethylamine to produce N,N,N-trimethyl-(1,1′-biphenyl)-2-methanaminium bromide; (c) N,N,N-trimethyl-(1,1′-biphenyl)-2-methanaminium bromide was converted to N,N-dimethyl-2-methyl-(1,1′-biphenyl)-3-methanamine in the presence of sodium amide and liquid NH_3 by Sommelet-Hauser



(a) NBS, TBHP, C_6H_6 (b) $N(CH_3)_3$, ethyl acetate (c) $NaNH_2$, $NH_3(l)$, NH_4Cl (d) $ClCOOC_2H_5$, C_6H_6

Scheme-II: Synthetic scheme of 3-(chloromethyl)-2-methyl-1,1'-biphenyl from 2-methyl-1,1'-biphenyl

rearrangement; and finally (d) N,N-dimethyl-2-methyl-(1,1′-biphenyl)-3-methanamine was chlorinated with ethyl chloroformate to get the target compound 3-(chloromethyl)-2-methyl-1,1′-biphenyl.

Liquid bromine is the most commonly used bromination reagent, which shows high reactivity in bromination reactions [10]. However, liquid bromine is hyper-toxic and corrosive, which may cause serious safety problems in industrial production. Therefore, NBS was selected as the bromination reagent. Although the reactivity of NBS is lower than liquid Br_2 in bromination, however, it is more environmental friendly and safer, and by-products are recyclable. The synthesis of 2-(bromomethyl)- 1,1′-biphenyl (**3**) by bromination of 2-methyl-1,1′-biphenyl (**2**) with NBS achieved the yield of 91.2 %. N,N,N-trimethyl-(1,1′-biphenyl)-2-methanaminium bromide (**4**) was synthesized by amination of 2-(bromomethyl)-1,1′-biphenyl (**3**) with trimethylamine, a very common and cheap raw material, which resulted in good yield of 98.0 %. After simple filtration and evaporation, the synthesized intermediates **3**, **4**, **5** and target compound **6** can be obtained with high purities (**3**: 85.6 %; **4**: 99.6 %; **5**: 96.4 %; **6**: 89.9 %) as determined by HPLC. The overall yield of the target compound **6** is 73.9 %.

Compared with the traditional synthetic process, present synthetic process is more facile and clean. Compound **4** was synthesized by bromination of compound **2** with NBS followed by ammoniation with trimethylamine, which avoided the use of high-toxic and high-risk reagents such as thionyl chloride, lithium aluminum hydride and methyl iodide. In addition, the synthesis of compound **4** was shortened to only two steps and achieved high yield (89.4 %). In summary, present synthetic procedure for 3-(chloromethyl)-2-methyl-1,1′-biphenyl (**6**) is more facile and environmental friendly, safer and suitable for mass production.

Conclusion

In the present work, a facile synthetic process for 3-(chloromethyl)-2-methyl-1,1′-biphenyl, a key intermediate for the preparation of bifenthrin is developed. 3-(Chloromethyl)-2-methyl-1,1′-biphenyl was synthesized from 2-methyl-1,1′-biphenyl through four steps, including bromination with NBS, amination with trimethylamine, Sommelet-Hauser rearrangement and chlorination with ethyl chloroformate. Compared with the traditional synthetic process of 3-(chloromethyl)-2-methyl-1,1′-biphenyl, present synthetic process exhibits several advantages, including simplicity in amination, simplicity in product purification, high overall yield (73.9 %) and environmental friendly. The synthetic process reported here represents a promising synthetic method for 3-(chloromethyl)-2-methyl-1,1′-biphenyl.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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