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Note

A convenient synthesis of Fenpyroximate

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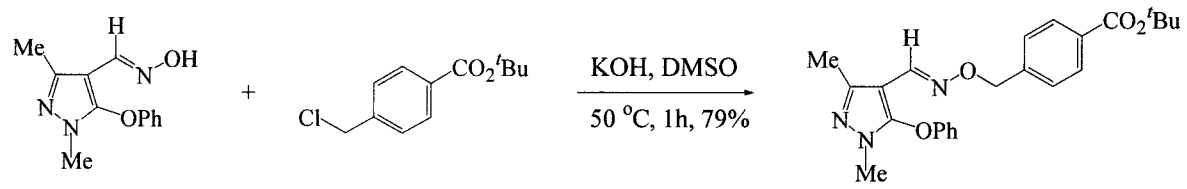
Abstract : Fenpyroximate was prepared by Williamson synthesis of 4-hydroxyimino-5-phenoxypyrazole and t-butyl 4-bromomethyl benzoate, while an efficient method for the synthesis of t-butyl benzoate still remains a challenging problem. We have found that t-butyl benzoate could be prepared from benzoic acid by the sulfuric acid-catalyzed reaction with isobutene via in situ generation from t-butanol. It has been proven that this process is more convenient for the preparation of t-butyl 4-bromobenzoate, thus allows a facile entry to fenpyroximate.(Received July 1, 2005; accepted September 24, 2005)

Key words : fenpyroximate, t-butyl 4-bromomethyl benzoate, benzoic acid, t-butanol.

Proton-translocating NADH:ubiquinone oxidoreductase (complex I) has been found as molecular target of new and structurally diverse inhibitors for agrochemical application. A wide variety of complex I inhibitors act at or close to the ubiquinone reduction site (Lümmen, 1998). Fenpyroximate was identified as the complex I inhibitor and introduced as the effective control agent against phytophagous mites, predacious mites, and animal parasitic and soil mites (Taninaka, 1993).

It was reported that fenpyroximate, tert-butyl (E)-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-p-toluate (1), was synthesized employing Williamson ether synthesis of 4-hydroxyiminomethyl-5-phenoxy-1,3-dimethylpyrazole (2) and t-butyl 4-chloromethyl benzoate (3), as shown in Scheme 1 (Hamaguchi et al., 1987). The known compound 2 was easily prepared and well-described in the literatures (Park et al., 2004; Holzer *et al.*, 2003), while the synthesis of 3 still needs an efficient preparing method. Thus, we paid a special attention in the preparation of t-butyl 4-halomethyl benzoate, which would offer more convenient synthesis of fenpyroximate. Here, we would like to report the efficient synthesis of t-butyl benzoate from the corresponding benzoic acid by the sulfuric acid-catalyzed reaction with isobutene via in situ generation from t-butanol.

Our initial research focused on preparation of t-butyl 4-bromomethyl benzoate (7), but we encountered a problem in the synthesis. It has been known that the ester formation of aromatic acids with tertiary or sterically hindered alcohols is especially ineffective even under severe conditions. Literatures showed that t-butyl toluate (5) was synthesized by the acylation, as depicted in Scheme 2, from p-toluoyl chloride (4) and t-butanol



2 **3** **1** (Fenpyroximate)

Scheme 1. Preparation of fenpyroximate

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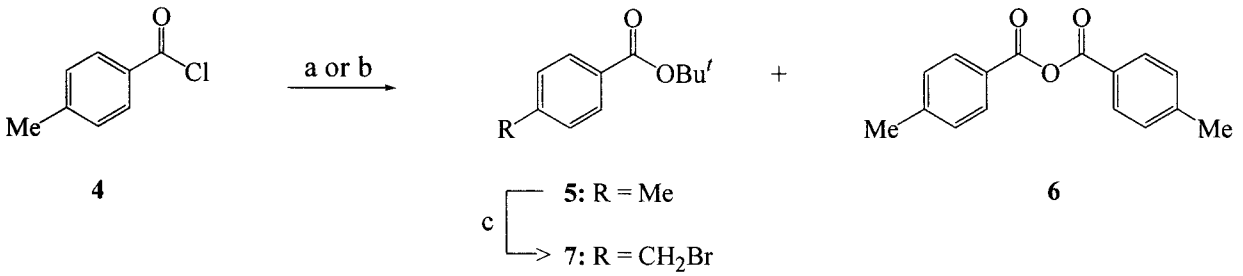
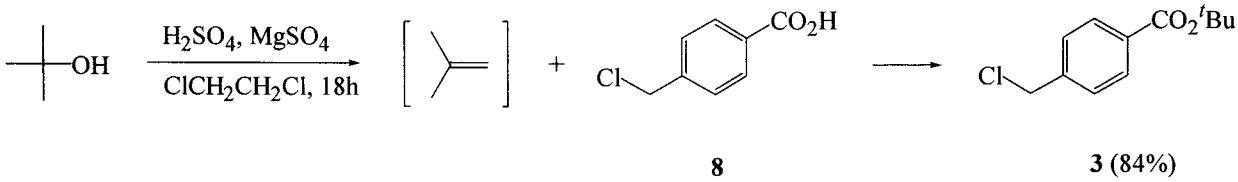


a) t-BuOH, pyridine, rt, 72h, 5 (56%) and 6 (12%); b) KOBu^t, THF, ice-bath, 2h, 5 (64%) and 6 (15%); c) NBS, Bz_2O_2, CCl_4, 50°C, 3h, 89%.

Scheme 2. Preparation of t-butyl 4-bromomethyl benzoate



Scheme 3. Improved synthesis of t-butyl 4-chloromethyl benzoate

in pyridine (Rosowsky et al., 1989) or 4 and lithium t-butoxide (Crowther et al., 1971), respectively. However, in both acylation reactions, we commonly observed the side product, p-toluic anhydride (6), in a considerable amount. Later, t-butyl p-toluate (5) was converted to t-butyl 4-bromomethyl benzoate (7) in 89% yield by the treatment of N-bromosuccinimide and benzoyl peroxide in carbon tetrachloride (Rosowsky et al., 1989).

Thus, we paid a special attention in the synthesis of t-butyl ester of benzoic acid, which would offer more convenient pathway to fenpyroximate. After several trials, we found that t-butyl 4-chloromethyl benzoate (3) could be prepared from the corresponding benzoic acid by sulfuric acid-catalyzed reaction with isobutene via in situ generation from t-butanol (Wright et al., 1997), as shown in Scheme 3. In a typical experiment, concentrated sulfuric acid (4 equiv) was added to a vigorously stirred suspension of anhydrous magnesium sulfate (4 equiv) in dichloroethane, and then 4-chloromethyl benzoic acid (8) (1 equiv) and t-butanol (5 equiv) were added. The reaction mixture was then closed tightly and stirred for 18 hr at room temperature, providing the desired t-butyl 4-chloromethyl benzoate (3) in 84% yield. It has been proven that this process is more efficient and convenient for the preparation of t-butyl 4-chloromethyl benzoate without any side-product, and superior to the previously described methods in Scheme 2, thus allows a facile entry to fenpyroximate.

The final installation to fenpyroximate was achieved by the Williamson synthesis from 4-hydroxyiminomethyl-5-phenoxy-1,3-dimethylpyrazole (2) and t-butyl 4-chloromethyl benzoate (3) in 79% yield, in the presence of potassium hydroxide in dimethylsulfoxide. The spectroscopic data and biological assay of the prepared fenpyroximate are identical to those reported in the literature (Hamaguchi et al., 1987).

Experimentals

Synthesis of t-butyl p-toluate (5). To a slurry solution of potassium t-butoxide (798 mg, 7.1 mmol) in THF (20 mL), 4 (1 g, 6.5 mmol) was added dropwise in an ice bath under the nitrogen atmosphere. The reaction mixture was allowed to stir for 2h at the same temperature. The solvent was removed and then partitioned with ethyl acetate (60 mL) and H_2O (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, and then evaporated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (hexane: ethyl acetate

= 9:1) to give the desired compound 5 (793 mg, 64 %) and the side-product 6 (248 mg, 15%). t-Butyl p-toluate (5): ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 2H, *J* = 12.3 Hz), 7.22 (d, 2H, *J* = 12.0 Hz), 2.39 (s, 3H), 1.58 (s, 9H). p-Toluic anhydride (6): ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 2H, *J* = 4.8 Hz), 7.312 (d, 2H, *J* = 4.8 Hz), 2.44 (s, 6H); MS (70eV) m/z (rel intensity), 254 (M+, 14), 226 (13), 119 (100), 91 (36), 65 (11).

Synthesis of t-butyl 4-chloromethyl benzoate (3). In a 500 mL round-bottomed flask, concentrated sulfuric acid (5.76 mL, 58.6 mmol) was added to a vigorously stirred suspension of anhydrous magnesium sulfate (28.2 g, 234.5 mmol) in dichloroethane (200 mL). The mixture was stirred for 15 minutes, after then 8 (10.0 g, 58.6 mmol) and t-butanol (21.73 g, 293.1 mmol) was added to this mixture. The reaction mixture was sealed tightly and stirred for 18h at room temperature. The reaction was then quenched with saturated sodium bicarbonate solution. The separated organic phase was washed with brine, dried over $CaCl_2$, and then evaporated under reduced pressure to give 3 (11.2 g, 84%) as an semi-solid: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2H, *J* = 8.2 Hz), 7.43 (d, 2H, *J* = 8.3 Hz), 4.60 (s, 2H), 1.59 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 23.3, 40.6, 76.3, 123.4, 125.0, 127.1, 136.8, 160.3; Anal. Calcd. for $C_{12}H_{15}ClO_2$: C, 63.58; H, 6.67. Found (Elemental Analysis): C, 63.74; H, 6.96; HRMS (EI) calcd for $C_{12}H_{15}ClO_2$: 226.0761 found : 226.0760.

Synthesis of Fenpyroximate (1). To a solution of 2 (0.3 g, 1.29 mmol) in DMSO (1.5 mL) was added KOH (93 mg, 1.67 mmol). The mixture was allowed to stir for 30 minutes at room temperature, after then 3 (0.29 g, 1.3 mmol) in DMSO (1 mL) was added to this mixture. The solution was stirred for 1h at 50°C. The reaction mixture was partitioned with ethyl acetate (60 mL) and H_2O (50 mL). The organic layer was washed successively with brine and water, dried over Na_2SO_4, and then evaporated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (hexane:ethyl acetate = 3:1) to give 1 (430 mg, 79%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 2H, *J* = 8.2 Hz), 7.82 (s, 1H), 7.26-7.33 (m, 4H), 7.11 (m, 1H), 6.87 (d, 2H, *J* = 7.9 Hz), 5.03 (s, 2H), 3.59 (s, 3H), 2.34 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (CDCl3) δ 16.0, 29.4, 35.4, 76.6, 82.2, 101.4, 116.5, 124.9, 129.1, 130.7, 131.2, 132.6, 142.3, 143.7, 148.2, 149.0, 158.0, 166.8; Anal. Calcd. for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found (Elemental Analysis): C, 67.10; H, 6.62; N, 9.56; HRMS (EI) calcd for $C_{24}H_{27}N_3O_4$: 421.2002 found: 421.2001.

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펜피록시메이트의 새로운 제조방법

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요약 : 살충제 펜피록시메이트는 4-hydroxyimino-5-phenoxypyrazole과 t-butyl 4-chloromethyl benzoate로부터 Williamson합성을 통하여 합성되고 있다. 그러나 t-butyl benzoate 의 효과적인 합성방법은 여전히 문제점으로 남아있다. 본 연구에서는 t-butyl benzoate를 황산 촉매에서 t-butanol로부터 생성되는 isobutene을 사용하여 4-chloromethyl benzoic acid에 부가하여 합성하였다. 이 방법은 부산물의 생성없이 t-butyl 4-chloromethyl benzoate을 합성할 수 있어 기존에 보고된 방법보다 훨씬 용이하다. 따라서 본 연구는 펜피록시메이트를 대량으로 합성하는 효과적인 방법을 제시하였다.

색인어 : 펜프록시메이트, t-부틸 4-클로로메틸벤조에이트, 4-클로로메틸벤조산, t-부탄올,

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