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One-pot synthesis of 6-bromo-4,4-dimethylthiochroman

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Abstract One-pot synthesis of 6-bromo-4,4-dimethylthiochroman from bromobenzene is reported. The crucial connection between the three steps is that the byproducts in the first two steps are used as the catalyst in the third step. Compared with the previous route, this approach is of low consumption and low pollution.

Keywords One-pot synthesis · 6-Bromo-4,4-dimethylthiochroman · Byproduct utilization · Heterocyclic · 1-Bromo-3-methylbut-2-ene

Introduction

6-Bromo-4,4-dimethylthiochroman is an important intermediate in the preparation of some medicines, for example tazarotene [1, 2], SSRT5 antagonists [3], and RAR-γ retinoid receptors [4]. The synthesis of 6-bromo-4,4-dimethylthiochroman has attracted much attention. It was first synthesized by Garst et al. [5] from benzenethiol and 1-bromo-3-methylbut-2-ene, which undergo cyclization and bromination (as shown in Scheme 1a). A few years later, a new route was proposed in which 4-bromobenzenethiol reacts with 2-methyl-1,3-butadiene or 3-methylbut-3-en-1-yl diphenyl phosphate, and subsequently self-cyclizes, as shown in Scheme 1b, to produce 6-bromo-4,4-dimethylthiochroman [3, 6, 7]. Frigoli et al. [7] also reported condensation of 4-bromobenzenethiol and 1-bromo-3-methylbut-2-ene, which led to 6-bromo-4,4-dimethylthiochroman after cyclization (as shown in Scheme 1c). Of all the routes, those which involve bromination of thiochroman give lower yields,

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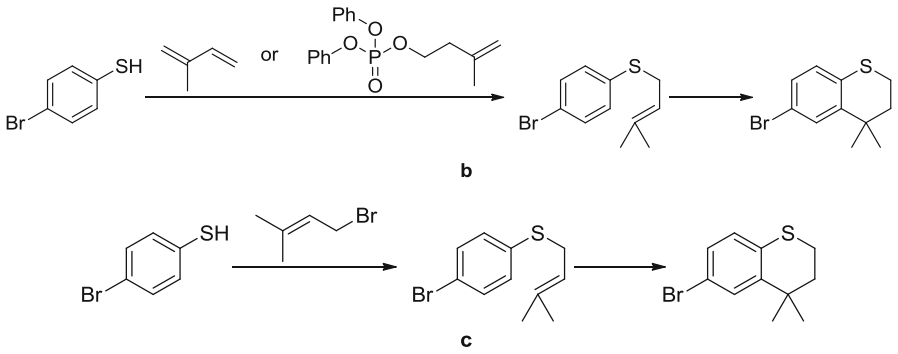
because side reaction is inevitable. 4-Bromobenzenethiol is, however, much more expensive than benzenethiol, limiting its utilization as the starting material. Recently, we found a one-pot method of preparation of 6-bromo-4,4-dimethylthiochroman which starts from bromobenzene and involves chlorosulfonation, reduction, etherization, and cyclization.

Results and discussion

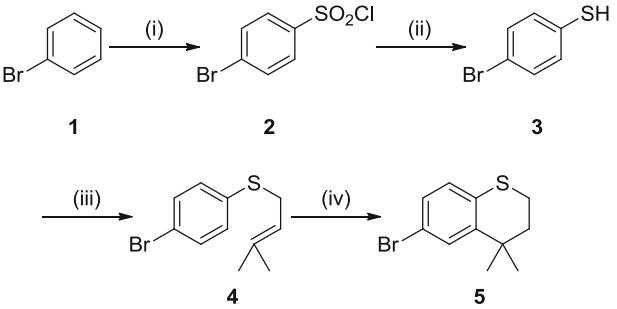
The whole process for preparation of 6-bromo-4,4-dimethylthiochroman is shown as Scheme 2. Compound **2** can be synthesized by chlorosulfonation of **1**. Previously reported chlorosulfonations of bromobenzene do not need a catalyst, but yields are not very good [8, 9]. In this work, sodium chloride was used as promoter to help increase the yield of **2**. Although there is no report of how this works, it is probable that addition of sodium chloride reduces the concentration of chloride ion so hydrolysis of **2** is inhibited.

Arylsulfonic chloride can be reduced by a variety of reagents, for example metals [10], hydrides [11, 12], and triphenylphosphorus [13]. Most of these reductants are efficient and convenient, but their effect on subsequent steps must be considered. Metals have less effect on etherization or cyclization; reduction using hydride is dangerous, because the system is strongly acidic and addition of hydride may lead to explosion; reduction using triphenylphosphorus is expensive and of low atom economy. Eventually, red phosphorus was selected as the reagent for reduction of **2**, because the yield of the reduction is good and the byproduct phosphoric acid can be used as catalyst in the cyclization.

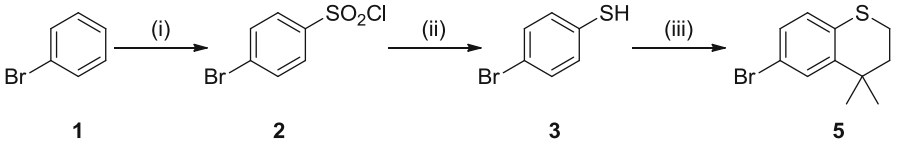
Step (iii) is favored by a basic environment, but the system is acidic after step (ii). Conversion cannot be very high because of the chemical equilibrium. However, the reaction can be propelled forward if one of the products is removed from the system. HBr is a byproduct in the etherization of **3** and 1-bromo-3-methylbut-2-ene, and the etherization will proceed continuously if the HBr is removed from the reaction mixture. Continuous purging with nitrogen is thus used to removed the HBr in step



Scheme 1 Synthesis of 6-bromo-4,4-dimethylthiochroman: **a** the route proposed by Garst et al., **b** the new route, **c** the route proposed by Frigoli et al



Scheme 2 Synthesis of 6-bromo-4,4-dimethylthiochroman. Reagents and conditions: (*i*) $ClSO_3H$/NaCl; (*ii*) I_2, P; (*iii*) 1-bromo-3-methylbut-2-ene; (*iv*) rapid step



Scheme 3 Synthesis of 6-bromo-4,4-dimethylthiochroman. Reagents and conditions: (*i*) $ClSO_3H$/NaCl; (*ii*) I_2, P; (*iii*) 1-bromo-3-methylbut-2-ene

(iii). Etherization in step (iii) obviously took longer than in a basic environment, but almost all the reactants were eventually converted. We also investigated the effect on etherization of the HCl produced in steps (ii) and (i). The results showed that both steps were favored by removal of HCl, so purging with nitrogen was also used in steps (ii) and (i).

Cyclization of **4** can be catalyzed by phosphoric acid, with methylsulfonic acid as solvent. Excess chlorosulfonic acid was added in step (i), and the byproduct was sulfonic acid. phosphoric acid was produced in step (ii). So additional reagents were not necessary in the cyclization step, and the experimental result proved our assumption. We did not separate intermediate **4** from the reaction mixture, because the product after adding 1-bromo-3-methylbut-2-ene in step (iii) was **5**. The probable reason was that sulfuric acid and phosphoric acid were already present in the reaction system, and intramolecular cyclization of **4** is a rapid step compared with the etherization. Thus the whole process can be regarded as three steps, as shown in Scheme 3.

Conclusion

In summary, we report a one-pot synthesis of 6-bromo-4,4-dimethylthiochroman from bromobenzene. The process comprises three steps, and the byproducts produced in steps (i) and (ii) are used as catalysts for step (iv). An additional promoter was added in step (i) to increase yield, and nitrogen purging was used throughout steps (i), (ii), and (iii) to propel the reactions forward. The approach

proposed in this work is convenient and, more importantly, of low consumption and pollution.

Experimental

The reactions were conducted in a batch reactor equipped with a buffer vessel and a tail gas absorption vessel to absorb the acidic gas produced in the reactions. The reaction mixtures were analyzed by GC and HPLC.

In the experiment we optimized the three steps independently and then combined them. In this section we describe the three independent steps and the one-pot process.

4-Bromobenzenesulfonic chloride (**2**)

Add 1 g NaCl (0.017 mol) to 8 g bromobenzene (0.051 mol), keep the temperature at 0–5 °C, add 20 g chlorosulfonic acid (0.172 mol) continuously in 4 h with nitrogen purging. Then increase the temperature to 25 °C and maintain this temperature until evolution of HCl ceases. The reaction mixture is then ready for the next step, or the product 4-bromobenzenesulfonic chloride can be obtained by adding the mixture to ice water and filtration. The isolated yield for this step is 94 % (13.2 g). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$–7.82 (m, 2H), 7.91–7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 128.9$, 131.2, 134.0, 144.1 [14].

4-Bromobenzenethiol (**3**)

Add 0.2 g iodine (0.79 mmol), 10 mL water, and 20 mL sulfuric acid to **2** at 20–30 °C, increase the temperature to 110 °C, add 2.5 g red phosphorus (0.08 mol) continuously in 1 h with nitrogen purging. Then increase the temperature to 140 °C and maintain this temperature for 5 h. The reaction mixture can then be cooled for the next step, or the product 4-bromobenzenethiol can be obtained by steam distillation. The isolated yield for this step is 96 % (8.5 g). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.46$ (s, 1H), 7.15 (d, 2H, $J = 8.6$), 7.38 (d, 2H, $J = 8.4$) [15]; MS (EI): *m*/*z* (rel. int.) 190 (40), 188 (40), 109 (100), 69 (26), 50 (19), 33 (10), 15 (3).

6-Bromo-4,4-dimethylthiochroman (**5**)

Add 10 mL water, 6.5 g phosphoric acid (0.066 mol), and 20 mL sulfuric acid to **3** at 20–30 °C then increase the temperature to 40 °C and add 6.7 g 1-bromo-3-methylbut-2-ene continuously within 1 h with nitrogen purging. Increase the temperature to 80–90 °C with vigorous stirring and maintain this temperature until evolution of HBr ceases. The final product can be obtained by pouring the mixture into ice water and filtration. The isolated yield for this step is 88 % (10.2 g). ^{1}H NMR (400 M Hz, $CDCl_3$): $\delta = 1.34$ (s, 6H), 1.95 (t, 2H), 3.04 (t, 2H), 6.96–7.48 (m, 3H), 7.28–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 19.4$, 20.7, 34.5, 44.1, 119.6, 120.1, 129.1, 129.7, 135.3, 140.8.

One-pot synthesis of 6-bromo-4,4-dimethylthiochroman

Add 1 g NaCl to 8 g bromobenzene (0.017 mol). Keep the temperature at 0–5 °C and add 20 g chlorosulfonic acid (0.172 mol) continuously over 4 h with nitrogen purging. Increase the temperature to 25 °C and maintain this temperature until evolution of HCl ceases (approx. 10 h). Slowly add 0.2 g iodine (0.79 mmol) and 10 mL water to the reaction mixture below 30 °C and then increase the temperature to 110 °C. Add 2.5 g red phosphorus (0.08 mol) continuously over 1 h, the increase the temperature to 140 °C and maintain for 5 h. Cool the reaction mixture to 40 °C and add 6.7 g 1-bromo-3-methylbut-2-ene continuously over 1 h with vigorous stirring. Then increase the temperature to 80–90 °C and maintain this temperature until evolution of HBr ceases (approx. 8 h). The final product can be obtained by pouring the mixture into ice water and filtration. The isolated yield for the whole process is 85 % (10.8 g).

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