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RESEARCH ARTICLE

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Synthesis and characterization of 5-bromo-3-sec-butyl-6-methyluracil

Abstract A new synthetic method for 5-bromo-3-*sec*-butyl-6-methyluracil (Bromacil) using 2-bromobutane and urea as starting materials is described. The synthesis involved condensation, cyclization and bromination with a total yield of 60%. The structure of Bromacil was determined by ^{1}H NMR, ^{13} C NMR and IR spectroscopy.

Keywords Bromacil, condensation, cyclization, bromination

1 Introduction

As an herbicide, 5-bromo-3-*sec*-butyl-6-methyluracil (trade name Bromacil) is mainly absorbed by the root, but it also exhibits herbicidal effects on broadleaf and deep-root weeds when it comes in contact with stems and leaves [1–3]. Bromacil is a nitrogen-containing heterocyclic compound which has a bromine substitute at the 5 position. It has high herbicidal activity and low toxicity. The synthesis of bromacil was developed mainly by the DuPont Corporation [4–7]. Its synthesis process is shown in Fig. 1: (1) the sec-butylamine is reacted with solid phosgene to give an isocyanate ester; (2) the isocyanate is reacted with methyl 3-aminocrotoacitate to produce uracil in the presence of sodium methoxide as catalyst; (3) finally, the 5-bromo-3-sec-butyl-6-methyluracil is obtained by bromination. This process has many problems: (1) Both *sec*-butylamine and solid phosgene are irritating substances with deleterious environmental effects. Solid phosgene easily deliquesces and the presence of residue in the reaction mixture reduces the purity of the product [8–12] (2) Sodium methoxide as catalyst has poor selectivity in cyclization; the four-ring formation is always in competition, resulting in reduced purity and yield [13,14]. (3) Bromination is done in a polar solvent using bromine. This leads to many byproducts and separation by column chromatography becomes necessary. The total yield is only 35% [15,16].

This report presents our improvement on the synthetic procedure based on the studies wherein 2-bromobutane was used as starting material for the first time [4,5]. The *sec*-butyl urea (I) obtained from reaction of 2-bromobutane and urea treated with ethyl acetoacetate is transformed into uracil (II) through direct cyclization in the presence of sodium hydride as a new catalyst. In the last step a selective reagent, a Pyr-HBr-Br_2 complex, is used in bromination with acetic acid and chloroform as solvents to come up with the final product Bromacil. This improved process reduces the reaction steps and also increases the yield. The synthetic route is presented in Fig. 2.

2 Experimental

2.1 Instruments and reagents

All reactions were monitored by TLC analysis and visualization was accomplished with WD-9403C ultraviolet (Beijing) apparatus. Melting points were determined using a WRS-1B digital melting point instrument (Shanghai). ^{1}H NMR was obtained on an AVENCE-400 MHz NMR (BRUKER) ($CDCl_3$ as solvent, TMS as internal standard), Infrared spectra were determined on an EVAN-11 Infrared Spectroscopy analyzer (BRUKER).

2-Bromine butane and urea are CP grade, the rest of the reagents are AR.

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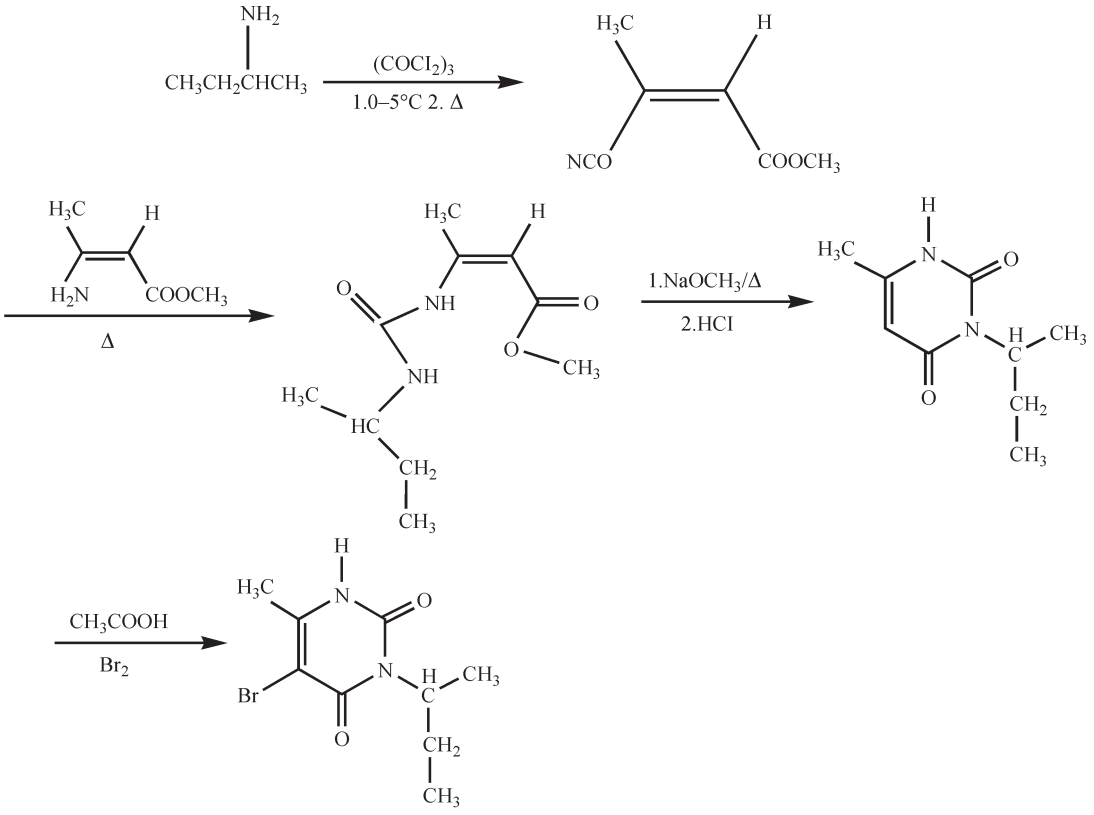

Fig. 1 Synthesis of Bromacil as described in Ref. [5]

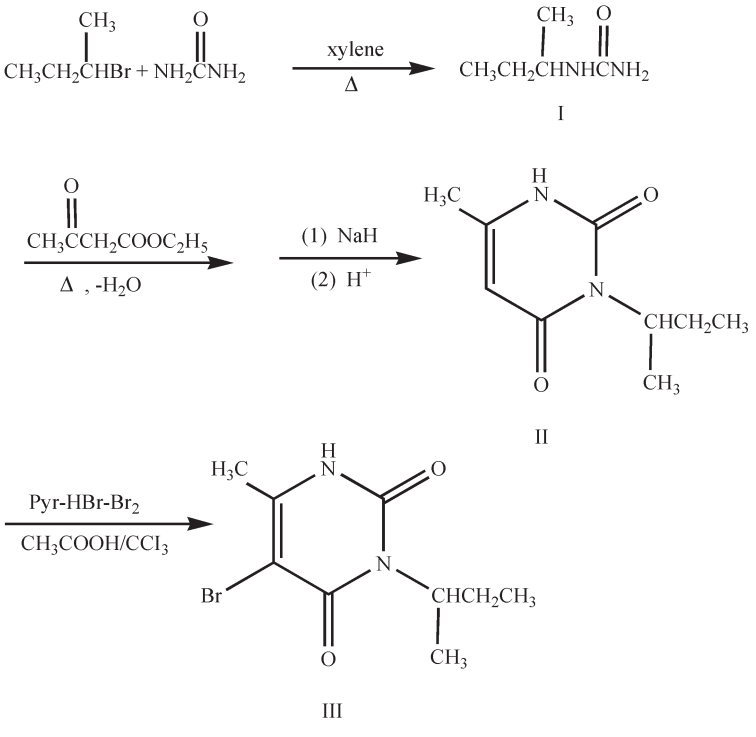

Fig. 2 New synthetic route for Bromacil

2.2 Synthesis of sec-butyl urea (I)

A solution of 2-bromobutane (27.4 g, 0.2 mol) in 150 mL xylene was mixed with urea (16.8 g, 0.3 mol). The reaction mixture was stirred under reflux for 8 h, until no raw materials were detected by TLC. Then the mixture was cooled to room temperature and filtered. The filtrate was washed with saturated aqueous salt (10 mL × 2), and dried with anhydrous sodium sulfate. After removing the solvent in vacuum, a solid was obtained. The residue was recrystallized from alcohol to give white crystals of *sec*-butyl urea. About 15.10 g of the solid was obtained for a yield of 86%. The sample was found to melt between 169°C and 171°C.

IR: (KBr, pellet, υ/cm^{-1}) 3425.35 (N–H), 1659.21 (C=O), 2974.23 (–CH_2, –CH_3); ^{1}H NMR (400 MHz $CDCl_3$) δ: 10.74 (s, 2H, –NH_2), 10.12 (d, 1H, –NH–), 3.85 (q, 1H, –CH–), 1.56 (m, 2H, –CH_2–), 1.68 (q, 3H, –CH_3), 0.96 (t, 3H, CH_3–CH_2–)ppm.

2.3 Synthesis of 3-*sec*-butyl-6-methyluracil (II)

sec-Butyl urea (I) (8.8 g ,0.1 mol) was dissolved in xylene (100 mL) and heated under reflux. Then 11.8 g (0.1 mol) of ethyl acetoacetate was added dropwise to the stirred reaction mixture for 30 min. The mixture was then refluxed for 5 h, until the reaction was completed, Sodium hydride (2.4 g ,0.1 mol) was added while the mixture was continuously stirred and refluxing continued for another 8 hours. The pH was adjusted to 3 by adding 20% hydrochloric acid. After cooling to room temperature, a crude solid was obtained which was then recrystallized using ethyl acetate-acetone (*V*: *V* = 3:1) to increased the purity of the 3-*sec*-butyl-6-methyluracil. A total of 16.2 g was obtained for a yield of 89.1%. IR: (KBr pellet, υ/cm^{-1}) 3457.2 (N–H stretching), 3099.9 (–CH_2, –CH_3), 1754.2 (α, β-unsaturated C=O), 1624.5 (–C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.78 (s, 1H, –NH), 2.43 (s, 3H, –CH_3), 2.21 (m, 2H, –CH_2–), 1.87 (m, 1H, –CH–), 1.76 (S, 1H, =CH–), 1.45 (d, 3H, –CH_3), 0.89 (t, 3H, in ethyl –CH_3) ppm.

2.4 Synthesis of 5-bromo-3-sec-butyl-6-methyluracil (III)

3-*sec*-Butyl-6-methyluracil (II) (18.2 g, 0.1 mol) was dissolved in 150 mL chloroform and 50 mL glacial acetic acid with constant stirring for 30 min at room temperature. After the mixture was cooled to 0°C (ice bath), the brominating reagent Pyr-HBr-Br_2 (60 mL) was added dropwise slowly. After 8 h at room temperature, TLC monitoring indicated that the reaction was complete. The solvent was evaporated under reduced pressure, producing a crude solid. The solid was recrystallized using acetone-ethyl acetate (*V*: *V* = 2:3). The purified product weighed 21.14 g giving a yield of 81%. The melting point was found to be 159–160°C. (lit[5]: 158–160°C).

IR: (KBr pellet, υ/cm^{-1}): 2878.3, 2938.6, 2945.7 (–CH_3), 1543.4, 2958.6, 2809. 3 (–CH_2), 1643.5 (C=C), 1721.0 (α, β-unsaturated C=O), 1657.3, 3289.5, 1523.4, 1321.3, 713.4 (amide), 577.5, 658.9 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) 1.79 (m, 1H, CH_2), 1.45 (dd, 3H, *J* = 6.89Hz, CH_3–CH), 0.86 (t, 3H, *J* = 7.43Hz, CH_3–CH_2); ^{13} C NMR δ: 159.35, 152.08, 147.74, 97.13, 52.38, 25.49, 19.37, 17.01, 10.839.

3 Results and discussion

3.1 Cyclization reaction

There is a competition between the formation of six- and four-member rings in the cyclization step (Fig. 3). Therefore, the choice of a suitable catalyst for the closed-loop reaction is very important. Compared to the original catalyst sodium methoxide, sodium hydride, although flammable, has the following advantages: (1) Sodium hydride is a stronger base than sodium methoxide. Thus, it is easier to activate the N atom using sodium hydride making it more capable of forming a stable six-member ring. (2) Formation of the reaction products is accompanied by the release of hydrogen and so the use of sodium hydride as catalyst can promote positive reaction, raising the yield. (3) The use of sodium hydride as catalyst makes possible one-pot synthesis of products (II), and reduces the reaction steps and the reaction time compared with those reported in references [5–6]. Experimental results showed that, under the same reaction conditions and with sodium methoxide as catalyst, the reaction is complete in 12 h and the yield of product III was 71.7%. However, in the case of sodium hydride the reaction was completed in only 8 h, and the yield was 89%.

3.2 Bromination reaction

The key to the synthesis of Bromacil is the reduction of byproduct formation during bromination. Because the reported reaction procedure used liquid bromine as bromination reagent, several problems are encountered. First, there is poor reaction selectivity. As the uracil is fairly reactive, it is difficult to avoid dibromination. Furthermore the products have very similar physical and chemical properties making separation by column chromatography necessary leading to the low yield of products. Second, as the use of liquid bromine is unsafe. By choosing a selective bromine complex as the brominating reagent and also regulating the co-solvent, yield and purity of the product can be improved greatly.

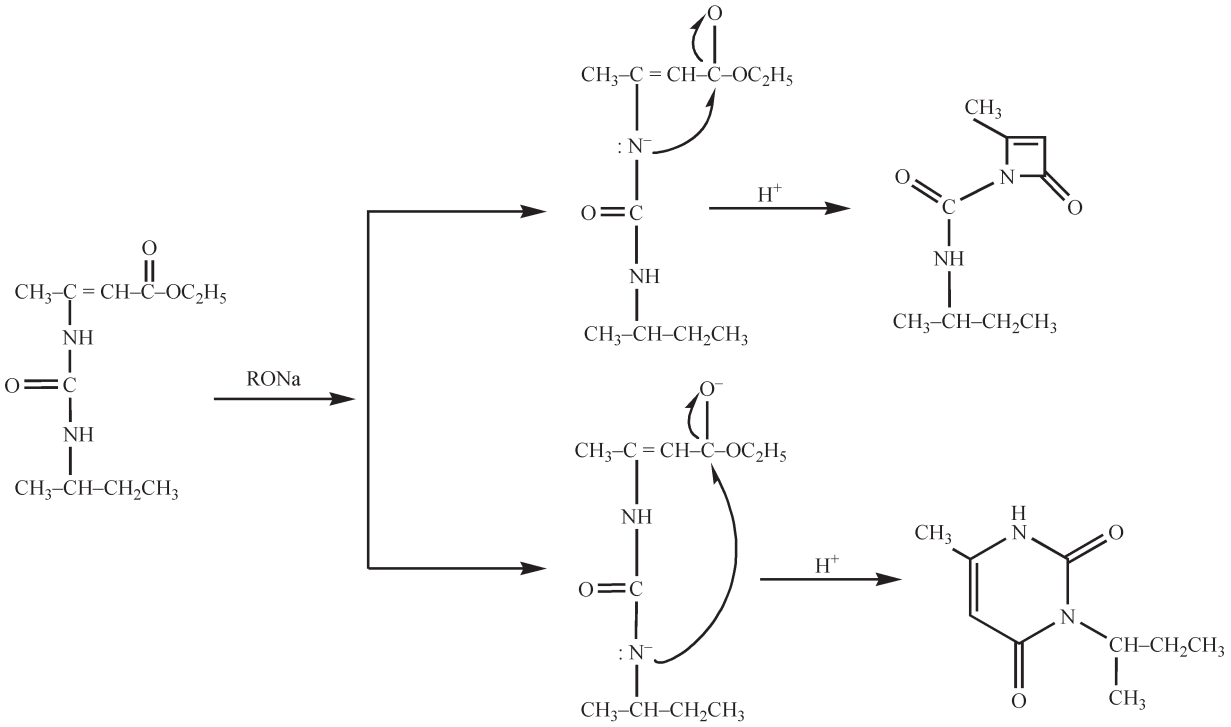

Fig. 3 Competing reaction between 4- and 6-member ring cyclizations

3.2.1 The choice of brominating reagent

According to the literatures [17–20], there are three types of brominating reagent that are suitable for a cyclic olefin. They are pyridinium hydrobromide perbromide (Pyr-HBr-Br_2), bromide dimethylbromide sulfur salt [$(CH_3)_2S^+$-$BrBr^+$], and *N*-bromo-animide compounds (NBS-DMF). We compared these three reagents and found that the pyridine-bromo-hydrobromide salt is the most suitable for a cyclohexene addition (Table 1).

Table 1 The influence of the brominating reagents on the yield of III

	types of brominating reagents		
	Pyr-HBr-Br_2	$(CH_3)_2S^+$-$BrBr^+$	NBS-DMF
yield of III/%	80.5	69.4	74.3

3.2.2 The influence of solvents on the bromination reaction

In bromination, acetic acid is usually employed as the polar solvent to promote the attacking by the bromine atoms. However, according to analysis of the structure of uracil, after bromine replaces a hydrogen atom of the aromatic ring the aromatic ring becomes slightly positive. Another bromine may add to the molecule to supply electrons. In order to enhance the single-bromide selective substitution reaction, solvents of lower polarity may be used. Through experiments, it has been shown that the use of aprotic solvents such as chloroform mixed with a small amount of acetic acid as co-solvent greatly improved the yield of the reaction (Table 2).

Table 2 The influence of solvents on the yield of III

	types of solvents			
	methanol	ethyl acetate	acetic acid	chloroform-acetic acid
yield of III/%	50.5	54.6	53.1	80.5

4 Conclusions

Compared to the procedure where sec-butylamine and solid phosgene are used as the raw materials, the method which uses 2-bromo-butane, urea and ethyl acetoacetate as main raw materials is more economical and more environment friendly. Through screening, we demonstrated that the use of sodium hydride instead of sodium methoxide as catalyst and the use of the bromination reagent Pyr-HBr-Br_2 instead of liquid bromine could increase the yield of the monobrominated product to 61%.

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