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A practical and convenient method for the synthesis of anesthetic drug thiopental: using thiourea and sodium ethoxide

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Abstract

A general, simple, practical and convenient method has been described for the synthesis of anesthetic drug thiopental using thiourea in the presence of sodium ethoxide. Anesthetic drug of thiopental was prepared in two stages; during the first stage, the alkylation of mthyl cyanoacetate was performed which was then to be followed by cyclization. Alkylation of methyl cyanoacetate which was performed by 2-iodopentane in the presence of sodium ethoxide reacts with thiourea and then the process was followed by thiopental prepration in excellent yield. Some important aspects of this methodology are the high reactivity of the substrates, avoidance of the use of hazardous solvents, simplicity of the product separation, low cost of the substrates and reagents and high yield of product. This is a applicable and efficient method for the preparation of thiopental anesthesia in high yield and in an appropriate time.

Keywords: Thiopental, drug, anesthetic, mthyl cyanoacetate, thiourea, synthesis.

Introduction

One of the most important inclinations of the researchers and the organic chemists is to find easier methods and processes which would be more economical for the synthesis of pharmaceutical compounds. Barbiturates are essential and important compounds in the areas of bio-chemistry, medicine and pharmaceutical. They are drugs that act as central nervous system depressants. One of these compounds is sodium thiopental which appears as a yellowish-white crystalline powder or a pale greenish hygroscopic powder

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with an alliaceous, garlic-like odor [1,2]. Thiopental is a sulphurous derivative of barbituric acid which can be identified by different commercial names such as pentotal, nesdonal, trapanal, phenobarbital, interval and pharmatal [3-7] (Figure 1).

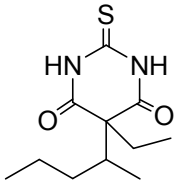
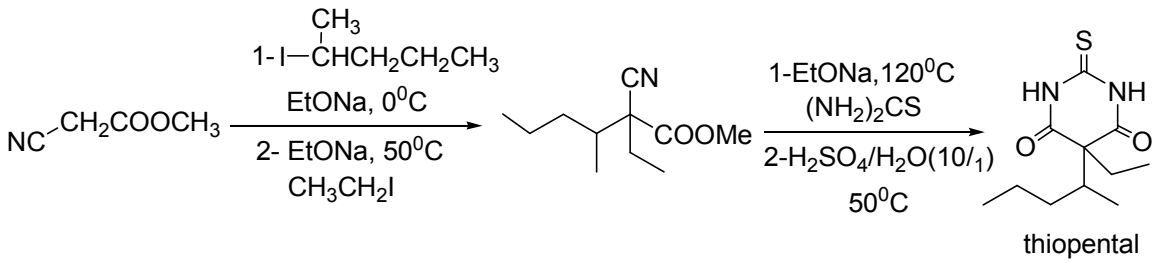


Figure 1. Structure of thiopental

Thiopental is a very important compound in the field of pharmaceuticals and medicine. Generally, thiopental is used in the induction of anesthesia and for the control of convulsive states [8-10]. It is also effective as anxiolytics [11], hypnotics [12], and anticonvulsants [13]. As it was already mentioned, we have various methods for the synthesis of thiopental. Generally, synthesis of thiopental is carried out by reactions of malonicester with thiourea in the presence of strong base, under reflux conditions and high temperatures [14]. Thiopental is synthesized by the alkylation of ethylmalonic ester with 2-bromopentane in the presence of sodium ethoxide [15,16]. The product ethyl-(1-methylbutyl) malonic ester undergoes heterocyclization with thiourea using sodium ethoxide as its base. In addition, thiopental is synthesized by alkylation of malonicester in the presence of strong bases such as KOH, pyridine and Ca $(OH)_2$ [17-19], and also by the treatment of ethyl cyanoacetate with methyl propyl ketone or propionaldehyde with malonicester [20,21]. Most of the above methods for the synthesis of thiopental have limitations like using very strong bases, low yields and long reaction times. Therefore, it is of great interest to find a simple and environmentally friendly method for the synthesis of thiopental. In this paper, we wish to describe a simple, efficient and useful method to prepare thiopental anesthesia which can overcome such kins of limitations. Therefore, we reported a practical and highly efficient method for the synthesis of thiopental by alkylation of malonicester followed by the cyclization with thiourea in the presence of sodium ethoxide (Scheme 1).



Scheme 1. Synthesis of thiopental

Experimental

General

Chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Melting points were determined by an Electrothermal 9100 apparatus. The FT-IR spectra were obtained on a FT-IR Perkin Elmber (Spectrum 100) spectrophotometer as KBr disks, or neat. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solution. The progress of the reaction was monitored by TLC using silica gel SILG/UV 254 plates. All products are known and characterized by comparison of their physical properties and spectroscopic data with those of the authentic samples.

Typical procedure for synthesis of methyl 2-cyano-3-methylhexanoate synthesis (1a): A constant mixture of methyl cyanoacetate (2 mmol, 180 mg) and sodium ethoxide (3 mL) was kept at 0 ^{0}C for 20 min. Then, 2-iodo pentane (2 mmol, 337 mg) was added slowly to the mixture and reaction continued at 0 ºC for 18 h. It is worth mentioning that, during the process, we did not shake the materials. The progress of reaction was monitored by TLC. After completion of the reaction, CH_2Cl_2 (15 mL) was added, and the mixture was washed with H_2O (3×10 mL). Then, the organic layer was isolated and was dried by anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give methyl 2-cyano-3-methylhexanoate which was purified by preparative TLC (silica gel, eluent *n*-hexane:EtOAc, 1:2) in order to obtain 125 mg of the pure methyl 2-cyano-3-methylhexanoate (74%).

Methyl-2-cyano-3-methylhexanoate(1a): **(**$C_9H_{15}NO_2$): Yield, (74%). ^{1}H NMR (250 MHz, $CDCl_3$): 0.9 (t, J^3= 7.4Hz, 3H, CH_3), 1.5 (m, 4H, CH_2), 1.7 (d, J^3= 1.75HZ, 3H, CH_3), 1.7-1.9 (m, 1H, CH, CH_2), 3.5 (s, 1H, CH), 3.8 (s, 3H, CH_3) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ= 13, 21, 24, 26, 43, 52, 53, 113, 164 ppm.

Typical procedure for synthesis of methyl 2-cyano-2-ethyl-3-methylhexanoate synthesis (1b): A mixture of methyl2-cyano-3-methylhexanoate (200 mg) and sodium ethoxide (3 mL) was vigorously stirred at 50 ºC for 15 min. Afterwards, ethyl iodide (2 mmol, 160 mg) was added to the mixture and our stirring was continued at 50 ºC for 180 min. The progress of reaction was monitored by TLC (*n*-hexane:EtOAc). After completion of the reaction, CH_2Cl_2 (15 mL) was added, and the mixture was washed with H_2O (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was

evaporated in vacuum to give methyl 2-cyano-2-ethyl-3-methylhexanoate which was then to be purified by preparative TLC (silica gel, eluent *n*-hexane:EtOAc, 1:2) to obtain 182 mg of the puremethyl2-cyano-2-ethyl-3-ethylhexanoate (92%).

Methyl-2-cyano-2-ethyl-3 methylhexanoate(1b)($C_{11}H_{19}NO_2$): Yield, (92%); ^{1}H NMR (250 MHz, $CDCl_3$): 0.9 (t, J^3= 7.5Hz, 3H, CH_3), 0.9 (t, 3H, CH_3), 1.5 (m, 4H, CH_2), 1.7 (d, J^3= 1.7Hz, 3H, CH_3), 1.7 (q, 2H, CH_2), 2.1 (m, 1H, CH), 3.9 (s, 3H, CH_3) ppm. ^{13}C NMR (62.5 Hz, $CDCl_3$): δ= 13, 19, 21, 24, 26, 28, 43,51, 53, 113, 164 ppm.

Typical procedure for synthesis of 5-ethyl-tetrahydro-6-imino-5-(pentan-2-yl)-2-thioxopyrimidin-4(1H)-one (1c): A mixture of methyl2-cyano-2-ethyl-3-methylhexanoate (250 mg) and thiourea dry (3 mmol, 162 mg) was added to sodium ethoxide (3 ml) in a kind of flask which was equipped with a condenser and then was heated at 20 ºC for 12 h. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered. Ethanol was removed by Distillation apparatus and the remaining mixture was further dried at 100 ºC for 2 h in vacuum drying oven. The isolated product was washed with H_2O (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4. In the next step, we evaporated the solvent in vacuum to take 202 mg of the pure 5-ethyl-tetrahydro-6-imino-5-(pentan-2-yl)-2-thioxopyrimidin-4(1H)-one (90%).

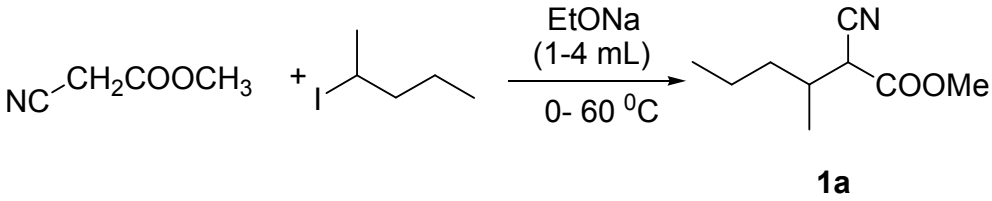
5-Ethyl-tetrahydro-6-imino-5-(pentan-2-yl)-2-thioxopyrimidin-4(1H)-one(1c): ($C_{11}H_{19}N_3OS$): Yield: (90%). ^{1}H NMR (250 MHz, $CDCl_3$): 0.9 (t, J^3= 12.5Hz, 6H, CH_3), 1.0 (d, J^3= 2.6Hz, 3H, CH_3), 1.1 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), 1.6 (q, 2H, CH_2), 2 (m, 1H, NH), 2.1 (m, 1H,CH), 7.3(s, 1H, NH), 7.6 (s, 1H, NH) ppm.^{13}C NMR (62.5, MHz, $CDCl_3$): δ= 10, 13, 14, 21, 29, 31, 34, 61, 137, 170, 173 ppm.

Typical procedure for synthesis of thiopental(1d): 5-Ethyl-tetrahydro-6-imino-5-(pentan-2-yl)-2-thioxopyrimidin-4(1H)-one (1c) (250 mg) was added to a mixture of H_2O (10 mL) and sulfuric acid (1 mL) in oil bath and at 50 ^{0}C under reflux conditions for 9 h. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered. Then, the product was isolated washed with H_2O (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give 231 mg of the pure thiopental (96%).

Thiopental (1d) ($C_{11}H_{18}N_2O_2S$): Yield: (%96). ^{1}H NMR (250 MHz, $CDCl_3$): 0.8 (t, J^3= 12.3Hz, 3H, CH_3) , 0.9 (t, J^3= 2.4Hz, 3H, CH_3), 1.0 (d, J^3= 1.75HZ, 3H, CH_3), 1.2 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 1.7 (q, 2H, CH_2), 2.1 (m, 1H, CH), 7.1 (s, 2H, NH) ppm.^{13}C NMR (62 MHz, $CDCl_3$): δ= 9, 14, 16, 20, 30, 31, 35, 61, 174, 177 ppm. FT-IR: 756(CS), 880 (CN), 1350(C-O), 1479(C=N), 1614(NH), 1694(C=O), 2961(C-H), 3234(N-H).

Result and discussion

Herein, we described an alternative and efficient method for the synthesis of thiopental in excellent yield. Anesthetic drug of thiopental would be prepared in two stages, alkylation of ester which was to be followed by cyclization of the mentioned product. In the first stage, in order to optimize the reaction conditions of alkylation of methyl cyanoacetate in terms of the amount of sodium ethoxide and temperature, the reaction of methyl cyanoacetate (2.0 mmol) with 2-iodo pentane (2.0 mmol) was studied as model reaction (Scheme 2).



1a

Scheme 2 .

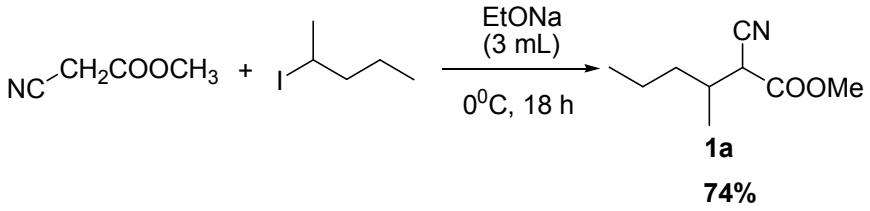
As we excpected, due to high reactivity of alpha hydrogen methyl cyanoacetate, corresponding product wasn't formed at temperatures higher than room temperature (Table 1, entries 1-3). As a result, we decided to study the reaction at temperatures lower than room temperature to reduce reactivity of alpha hydrogen methyl cyanoacetate (Table 1, entries 4-9).

As can be seen from Table 1, the rate and efficiency of reactions depend on the amount of sodium ethoxide and temperature. The best results were obtained in the presence of sodium ethoxide (3 mL) (Table 1, entry 6) at 0 ºC (Scheme 3).

Table 1. Optimization of sodium ethoxide (EtONa) amount and temperature of reaction to synthesis methyl 2-cyano-3-methylhexanoate [a]

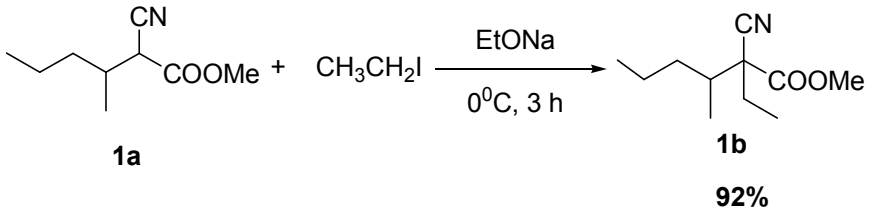
Entry	EtONa (ml)	Temp ^{0}C	Time (h)	**(1a)** Yields [b] %
1	1	60	3	----
2	1	50	5	----
3	1	40	7	----
4	1	r.t	10	20
5	1	10	17	64
6	1	0	28	78
7	2	0	39	75
8	3	0	18	88 *
9	4	0	18	79

[a]Model reaction conditions: molar ratio of methyl cyanoacetate / 2-iodo pentane was (2.0 mmol) / (2.0 mmol). The reactions run in the presence of sodium ethoxide under mild conditions. [b] Yield refer to an isolated yield by preparative chromatography.



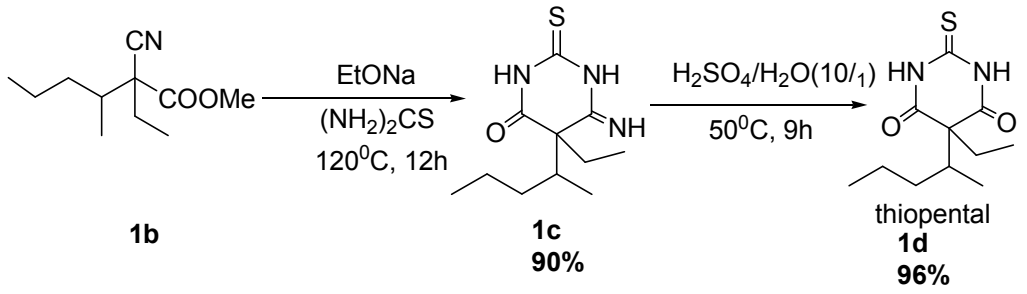
Scheme 3.

During the second stage of alkylation, methyl2-cyano-2-ethyl-3-methylhexanoate (2a) was prepared in 92% yield from the treatment of 1a with ethyl iodide at 50 ^{0}C in the presence of sodium ethoxide (Scheme 4).



Scheme 4.

After performing the alkylation stage, we used thiourea for cyclization process (Scheme 5). 1c was prepared in 90% yield from reaction of thiourea with 1b at 120 ^{0}C and in the presence of sodium ethoxide. In the last stage, thiopental (1d) was synthesized in very high yield. Moreover, thiopental was easily prepared from the treatment of 1c with a mixture of sulfuric acid and H_2O with ratio(10:1)



1b **1c** **90%** **1d** **96%**

Scheme 5.

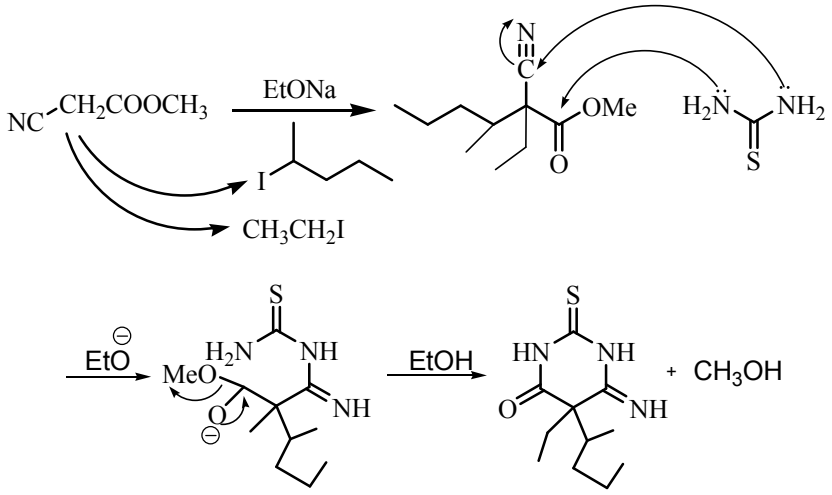


Figure 2. Proposed mechanism for synthesis of thiopental.

Conclusion

In conclusion, we described an efficient, practical, non-corrosive, inexpensive and environmentally friendly method for the preparation of anesthetic drug thiopental. Alkylation of methyl cyanoacetate followed by the cyclization step, obtained the corresponding thiopental in excellent yield. Some important benfities of this methodology in comparison to other methods are the high reactivity of the substrates, its avoidance to use the hazardous solvents, simplicity of the product separation, low cost of the substrates and reagents and high yield of product.

Acknowledgments

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