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A novel synthesis of benzo[*b*]thiophene

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Abstract We report a convenient method of preparation of benzo[*b*]thiophene, using 2-chlorobenzaldehyde and 2-mercaptoacetonitrile as starting materials. The process comprises two steps, neither of which has been reported previously. The reactions in this work are clean and efficient.

Keywords Benzo[*b*]thiophene · Coupling · Decyanation

Introduction

Benzo[*b*]thiophene and its derivatives are important, because they are widely used in the preparation of, for example, medicines [1–5], pesticides [6, 7], and semiconductors [8, 9]. Benzo[*b*]thiophene can be synthesized by benzene ring closure or thiophene ring closure. Kitamura et al. [10] reported the synthesis of benzo[*b*]thiophene by cyclization of (2-(2-bromovinyl)phenyl)(methyl)sulfane; Rudzki et al. [11] synthesized benzo[*b*]thiophene from ((2-bromophenyl)ethynyl)trimethylsilane via cyclization with sodium sulfide; Voronkov et al. [12] reported the synthesis of benzo[*b*]thiophene by cyclization of (1,2-dichloroethyl)benzene and hydrogen sulfide; Denyagina et al. [13] reported cyclization of bromobenzene, ethyne, and hydrogen sulfide to give benzo[*b*]thiophene; Reinecke et al. [14] reported two-step benzene ring closure using thiophene-2,3-dicarboxylic acid as the starting material. There are also many other methods of preparation of benzo[*b*]thiophene [15–19]; for these, however, yields are much lower.

We recently found a new method of preparation of benzo[*b*]thiophene using 2-chlorobenzaldehyde and 2-mercaptoacetonitrile as starting materials.

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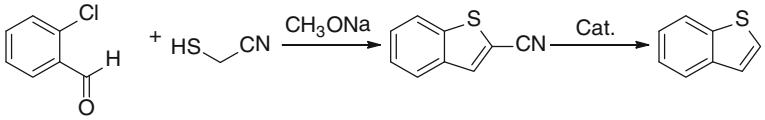
Result and discussion

The whole process can be illustrated by the following scheme:



The first step is coupling between 2-chlorobenzaldehyde and methanethiol substituted with an electron-withdrawing group; similar coupling has been reported elsewhere. Brouwer [20] reported the coupling between 2-chlorobenzaldehyde and 2-mercaptoacetic acid, which gives benzo[*b*]thiophene-2-carboxylic acid. The process is efficient (benzo[*b*]thiophene-2-carboxylic acid can be obtained with 87.6 % yield) but consumes much alkali and produces too much waste water. In this work we replaced the carboxyl group with cyano, and were surprised when the result of coupling was 2-cyanobenzo[*b*]thiophene in comparable yield at lower temperature.

The second step is a decyanation reaction, which has also been reported before. Weigert et al. [21] reported hydrodecyanation using Pd as catalyst, but this reaction is limited because hydrogen cyanide is produced. Yuzawa et al. [22] reported decyanation with Pt/TiO_2 as catalyst and ammonia as reagent, so the hydrogen cyanide was bound as soon as it was produced. In this work we used a combination of hydrogen and ammonia as the reagent, and Pd/TiO_2 and Cu as catalyst, and the reaction was complete in a shorter time.

The effect of reaction conditions on yield was investigated. For the cyclization step, several bases were used and compared. The effects of temperature and reagent ratio on yield of 2-cyanobenzo[*b*]thiophene were also examined. The results are listed in Table 1. Use of other bases, for example NaOH, Na_2CO_3, and KOH, resulted in much poorer performance than CH_3ONa. The cyclization process includes dehydration, and reaction between hydroxide and 2-mercaptoacetonitrile also produces water, which prevents progress of the cyclization. Also, NaOH, Na_2CO_3, and KOH are weak bases compared with CH_3ONa, so condensation proceeds slowly. Comparison of entries 2, 5, 6, and 7 shows that the optimum temperature for the reaction is 85 °C; at this temperature the rate of cyclization is favored and byproducts are diminished. The molar ratio of 2-chlorobenzaldehyde to CH_3ONa has a substantial effect on the reaction, probably because less CH_3ONa cannot keep the reaction environment sufficiently basic to favor the condensation reaction, whereas too much CH_3ONa results in conversion of the cyano group to carbonyl via alcoholysis.

In the decyanation step, two other catalysts, Pd and Pt/TiO_2, were selected for comparison, and the effect of reaction temperature on the yield of benzo[*b*]thiophene was also investigated. The results are listed in Table 2, from which it is apparent that the catalyst used in this work is more efficient than those used in previous work. The probable reason is that both Pd and Pt are of high catalytic activity in hydrogenation, whereas Cu is more active in catalysis of rupture of the C–CN bond, because the cyano group has chemical properties similar to those of halogen atoms. The reaction temperature also substantially affects the yield of benzo[*b*]thiophene. Low temperature reduces the rate of the reaction whereas if the temperature is too high the yield of byproducts is increased.

Table 1 Effect of reaction conditions on the yield of 2-cyanobenzo[*b*]thiophene

Entry	Base used	Temperature (°C)	*n*(2-chlorobenzaldehyde):*n*(CH_3ONa)	Yield[a] (%)
1	NaOH	85	1:1.2	20.3
2	CH_3ONa	85	1:1.2	85.4
3	Na_2CO_3	85	1:1.2	21.7
4	KOH	85	1:1.2	21.5
5	CH_3ONa	55	1:1.2	45.8
6	CH_3ONa	75	1:1.2	79.5
7	CH_3ONa	95	1:1.2	84.1
8	CH_3ONa	85	1:1.0	67.9
9	CH_3ONa	85	1:1.5	75.5

Reaction conditions: 3 h

[a] Isolated yield

Table 2 Effect of reaction conditions on the yield of benzo[*b*]thiophene

Entry	Catalyst	Temperature (°C)	Yield[a] (%)
1	Pd	250	80.3
2	Pt/TiO_2	250	79.5
3	Pd/TiO_2-Cu	250	90.2
4	Pd/TiO_2-Cu	200	78.8
5	Pd/TiO_2-Cu	300	80.4

Reaction conditions: in autoclave, 0.5 MPa hydrogen, 4 h

[a] Isolated yield

Conclusion

We report a convenient method for preparation of benzo[*b*]thiophene, using 2-chlorobenzaldehyde and 2-mercaptoacetonitrile as the starting materials. The process comprises two steps, coupling and decyanation, neither of which has been reported previously. The reactions in this procedure are clean and efficient.

Experimental

The reactions were carried out in a batch reactor. The reaction mixtures were analyzed by HPLC.

2-Cyanobenzo[b]thiophene

To 20 mL toluene, add 7 g 2-chlorobenzaldehyde, 3.3 g sodium methoxide, and 3.7 g 2-mercaptoacetonitrile. Increase the temperature to 85 °C and maintain for 3 h. When the reaction is complete, filter, then remove the solvent under vacuum. A solid mixture which contains mainly 2-cyanobenzo[*b*]thiophene is obtained. Pure

2-cyanobenzo[*b*]thiophene can be separated by use of column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.51 (m, 2H), 7.79–7.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 141.0$, 137.1, 133.2, 127.2, 124.7, 124.4, 121.5, 114.3, 108.8 [23].

Benzo[b]thiophene

In an autoclave, mix the solid mixture obtained in the last step, 0.5 g Pd/TiO_2 (5 %), 1 g Cu powder, 20 mL toluene, and 20 mL aqueous ammonia solution (20 %). Replace the air in the autoclave with hydrogen and increase the pressure to 0.5 MPa. Increase the temperature to 250 °C and maintain for 4 h. When the reaction is complete, cool, separate the organic layer, and wash it with dilute hydrochloric acid. Remove the solvent from the organic layer under vacuum to give 2.6 g benzo[*b*]thiophene, 77 % yield (98 % purity). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.90$–7.87 (m, 1H),7.81–7.78 (m, 1H), 7.41 (d, $J = 5.4$ Hz, 1H), 7.38–7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 138.9$, 138.7, 126.1, 124.4, 124.2, 123.7, 123.4, 121.8 [24].

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References

1. S. Dadiboyena, Eur. J. Med. Chem. **51**, 17–34 (2012)
2. P.S. Shinde, S.S. Shinde, A.S. Renge, G.H. Patil, A.B. Rode, R.R. Pawar, Lett. Org. Chem. **6**(1), 8–10 (2009)
3. S.M.N. Efange, D.C. Mash, A.B. Khare, Q.J. Ouyang, J. Med. Chem. **41**(23), 4486–4491 (1998)
4. F. Burkamp, S.R. Fletcher, J. Heterocyclic Chem. **39**(6), 1177–1187 (2002)
5. S. Galiano, O. Erviti, S. Perez, A. Moreno, L. Juanenea, I. Aldana, A. Monge, Bioorg. Med. Chem. Lett. **14**(3), 597–599 (2004)
6. D.P. Mcdonnell, D.L. Clemm, T. Hermann, M.E. Goldman, J.W. Pike, Mol. Endocrinol. **9**(6), 659–669 (1995)
7. B.K. Moorthy, J. Indian Chem. Soc. **67**(11), 909–911 (1990)
8. B. Wex, B.R. Kaafarani, A.G. Oliver, J.A.K. Bauer, D.C. Neckers, J. Org. Chem. **68**(21), 8258–8260 (2003)
9. M.M. Payne, S.A. Odom, S.R. Parkin, J.E. Anthony, Org. Lett. **6**(19), 3325–3328 (2004)
10. T. Kitamura, S. Kobayashi, H. Taniguchi, Chem. Lett. **10**, 1637–1638 (1988)
11. T. Kashiki, S. Shinamura, M. Kohara, E. Miyazaki, K. Takimiya, M. Ikeda, H. Kuwabara, Org. Lett. **11**(11), 2473–2475 (2009)
12. M.G. Voronkov, E.N. Deryagina, M.A. Kuznetsova, Zh. Org. Khim. **20**(7), 1591–1592 (1984)
13. E.N. Deryagina, N.A. Korchevin, E.N. Sukhomazova, N.V. Russavskaya, M.G. Voronkov, Zh. Org. Khim. **29**(11), 2246–2250 (1993)
14. M.G. Reinecke, J.G. Newsom, L.J. Chen, J. Am. Chem. Soc. **103**(10), 2760–2769 (1981)
15. C.L. Li, X.G. Zhang, R.Y. Fang, P. Zhong, J.H. Li, J. Org. Chem. **75**(20), 7037–7040 (2010)
16. M. Prats, C. Galvez, L. Beltran, Heterocycles **34**(5), 1039–1046 (1992)
17. M.G. Voronkov, E.N. Deryagina, E.N. Sukhomazova, N.K. Gusarova, G.G. Efremova, B.A. Trofimov, Zh. Org. Khim. **19**(6), 1221–1224 (1983)
18. M.G. Voronkov, E.N. Deryagina, E.N. Sukhomazova, Zh. Org. Khim. **18**(8), 1736–1743 (1982)
19. M.G. Voronkov, E.N. Deryagina, M.A. Kuznetsova, Zh. Org. Khim. **18**(8), 1743–1749 (1982)
20. W. G. Brouwer, Preparation of benzo[*b*]thiophene-2-carboxylic acids. WO9947510, (1999)
21. F.J. Weigert, M. Moguel, J. Mol. Catal. **75**(2), 209–218 (1992)
22. H. Yuzawa, H. Yoshida, Chem. Commun. **46**(46), 8854–8856 (2010)
23. S.L. Zhou, K. Junge, D. Addis, S. Das, M. Beller, Org. Lett. **11**(11), 2461–2464 (2009)
24. N. Barbero, R. Martin, Org. Lett. **14**(3), 796–799 (2012)