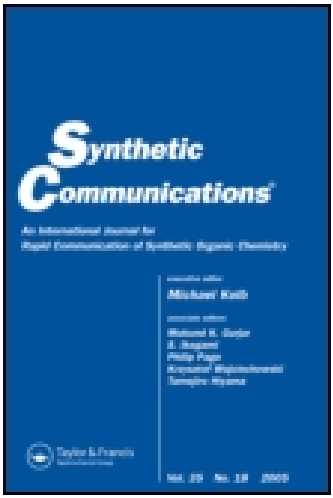

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Synthesis of Multi-Substituted Benzothiophenes: An Application of Alder-Rickert Reaction

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SYNTHESIS OF MULTI-SUBSTITUTED BENZOTHIOPHENES: AN APPLICATION OF ALDER-RICKERT REACTION

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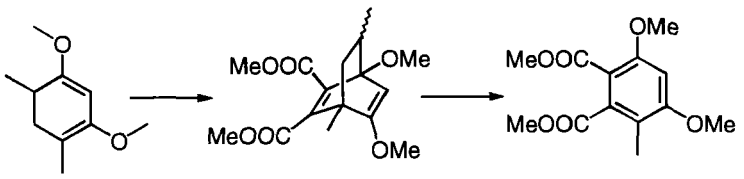
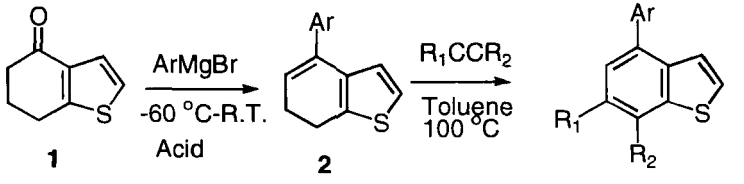
A short synthesis of multi-substituted benzothiophenes using the Alder-Rickert reaction is described.

The Alder-Rickert reaction has been widely used in the construction of polysubstituted benzenes since its discovery, six decades ago.[1] Readily available cyclohexanedienes derived from 1,3-cyclohexanediones have been recently used in the synthesis of multisubstituted phenol derivatives (eqn. 1).[2] Surprisingly, however, this powerful method has not been taken advantage in the preparation of polysubstituted fused heterocycles, such as benzofurans, benzothiophenes and indoles. Although a number of methods are available for the preparation of various substituted benzoheterocycles, multi-substituted benzoheterocycles still pose a challenge to synthetic organic chemists.[3-6] As such ring systems are found in a large number of biologically active compounds, there appears to be a need for short method for the preparation of this class of compounds.



eqn. 1

The commercially available 4-keto-4,5,6,7-tetrahydrothianaphthene **1** has been utilized as a precursor for the synthesis of a variety of benzothiophenes.[7] The addition of Grignard reagents to the keto-group, followed by dehydration of the carbinol and further oxidation of the resulting diene (**2**), provides 4-substituted benzothiophenes.[7] Similarly, 3-vinylthiophenes also undergo Diels-Alder reaction with dienophiles, such as maleic and phthalic anhydrides.[8] The photocyclization of 3-vinylthiophenes has also been reported in the literature.[9] However, to date, the Alder-Rickert type cycloaddition reaction of dienes, such as **2** with dienophiles to generate benzothiophenes as illustrated in equation 2 has not been reported.



1 **2**

2a Ar = Ph
2b = 4-ClPh
2c = 4-FPh

3-10

eqn. 2

This paper demonstrates the use of the Alder-Rickert reaction for the preparation of multi-substituted benzothiophenes.

4-Keto-4,5,6,7-tetrahydrothianaphthene (**1**) was treated with two equivalents of phenylmagnesium bromide solution at -60 °C and was quenched with dilute hydrochloric acid. The diene **2a** was formed in 86 % yield by spontaneous dehydration of the intermediate carbinol during the work-up of the reaction. The diene **2a** was then treated with ethyl propiolate (two equivalents) in toluene at reflux for 24 hours. After chromatographic purification, 50 % of the diene was recovered and the desired product was obtained in 40 % yield (entry 1, Table). Attempts to drive this reaction to completion either by prolonged heating or by the

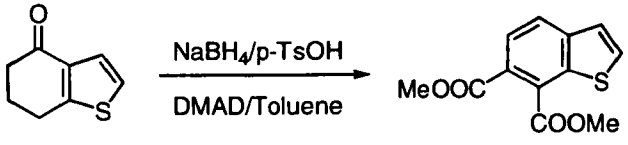
Table . Alder-Rickert synthesis of Benzothiophenes according to equation 2.[a]

Entry	Diene	R_1	R_2	Product	% Yield
1	2a	H	COOEt	3	40
2	2a	COOMe	COOMe	4	83
3	2a	H	COMe	5	75
4	2b	H	COOEt	6	73
5	2b	COOMe	COOMe	7	69
6	2b	H	COMe	8	52
7	2b	COPh	COPh	9	65
8	2c	H	COOEt	10	70

[a]All the reactions were carried out in toluene at reflux temperature for 24h with two equivalents of dienophile. All are isolated yields and are not optimized.

addition of dienophile were unsuccessful. Diene **2a** provided excellent yields of the product with dimethyl acetylenedicarboxylate (entry 2) and 3-butyn-2-one (entry

3) and all the diene being consumed in 24 hours. The reaction proceeded well with the diene **2b and 2c** (entries 4-8). In cases where two regioisomers (6- and 7-substituted) are possible. (e.g., with ethyl propiolate and 3-butyn-2-one), the Alder-Rickert reaction provided only the 7-substituted compound. The assignment is based on the large coupling constant (j = 8.1Hz) observed between the adjacent proton of the phenyl ring. Ethyl phenylpropiolate, phenylacetylene and methyl butynoate failed to undergo cycloaddition reaction with diene **2** as evidenced by the recovery of the starting materials. 6,7-Bis(methoxycarbonyl)benzothiophene **11** can also be prepared by this method as illustrated in equation 3. The intermediate carbinol obtained by the reduction of **1** with sodium borohydride furnished the desired benzothiophene after the treatment with dimethyl acetylenedicarboxylate in the presence of a catalytic amount of p-TsOH in refluxing toluene in 40 % overall yield. The reaction with other dienophiles was sluggish, however.



eqn. 3

In summary, we have shown that, the Alder-Rickert reaction can be applied to a short synthesis of highly functionalized benzothiophenes which are otherwise difficult to obtain.

Experimental Section

^{1}H NMR were obtained on a Bruker ACF-300 spectrometer. Chemical shifts are

reported in parts per million (δ scale) relative to tetramethylsilane as internal standard. IR spectra were recorded on a Pye-Unicam 3-200 spectrometer. Melting points were recorded on a Mettler-FP90 with FP81 cell and are uncorrected. Flash chromatography was performed on a 230-400 mesh silica gel.

General Procedure for the preparation 4-Aryl-6,7-dihydrobenzothiophenes: The preparation of 4-phenyl-6,7-dihydrobenzothiophene (**2a**) is representative: To a solution of 4-keto-4,6,7,8-tetrahydrothianaphthene (**1**) (2g, 13.7 mmol) in dry THF (30 mL) at -60 °C was added phenylmagnesium bromide (26mL, 26.0 mmol, 1M solution in THF) and the mixture was allowed to stir for 30 min. The reaction mixture was allowed to warm to 0 °C over 15 min and stirred at that temperature for 30 min. The reaction mixture was cooled to -60 °C , quenched with dilute hydrochloric acid , warmed to room temperature and extracted with ethyl acetate(2x100ml). The combined ethyl acetate layer was washed with brine, dried (Na_2SO_4) and concentrated. The oil was purified by flash chromatography (hexanes) to obtain the alkene **2a** (2.5g, 11.8 mmol, 86%): oil; ^{1}H NMR ($CDCl_3$) δ 7.45-7.3 (m, 5H), 7.00 (d, J = 5.1 Hz, 1H), 6.84 (d, J = 5.1 Hz, 1H), 5.88-5.85 (t, 1H), 2.93-2.87 (t, 2H), 2.55-2.48 (m , 2H); Calcd. for $C_{14}H_{12}S$ (212.31): C, 79.20; H, 5.70. Found: C: 78.94; H. 5.63

4-(4-Chlorophenyl)-6,7-dihydrobenzothiophene (2b): oil (80 %); ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 4H), 7.01 (d, J = 5.1 Hz, 1H), 6.79 (d, J = 5.1 Hz, 1H), 5.87-5.84 (t, 1H),2.932.88 (t, 2H), 2.55 -2.48 (m, 2H); Calcd. for $C_{14}H_{11}ClS$ (246.76): C,68.14; H, 4.49. Found: C, 68.35; H, 4.42.

4-(4-Fluorophenyl)-6,7-dihydrobenzothiophene (2c) : mp 81.3-82.6 (hexane); ^{1}H NMR ($CDCl_3$) δ 7.45-7.33 (m, 2H), 7.09-6.81 (m, 3H), 6.81 (d, J = 5.1 Hz, 1H), 5.86-5.83 (t, 1H), 2.95-2.89 (m, 2H), 2.57-2.5 (m, 2H); Calcd. for $C_{14}H_{11}FS$ (230.30): C, 73.01; H, 4.81. Found: C, 73.13, H, 4.71.

General Procedure for the Alder-Rickert reaction: The reaction between **2a** and ethyl propiolate is representative: A mixture of **2a** (1g, 4.7 mmol) and ethyl propiolate (1g, 10 mmol) in toluene (10 mL) was heated at reflux for 24 hours. The reaction mixture was cooled, concentrated and purified by flash chromatography (0-3% acetone/hexane) to obtain 7-ethoxycarbonylbenzothiophene **(3)** (0.53g, 40%): mp 94.6-95.2 (hexane/ethyl acetate); IR (KBr) 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 1H, J = 6.7 Hz), 7.60-7.41 (m, 8H), 4.55-4.48 (q, 2H), 1.56-1.46 (t, 3H). Anal. Calcd. for $C_{17}H_{14}O_2S$ (282.36): C, 72.31; H, 5.00. Found: C, 72.43; H, 5.05.

6,7-Bis(methoxycarbonyl)-4-phenylbenzothiophene (4): mp 95.8-96.4 °C. IR (KBr) 1724 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 7.67-7.5 (m, 8H), 4.03 (s, 3H), 3.95 (s, 3H); Anal. Calcd. for $C_{18}H_{14}O_4S$ (326.37): C, 66.24; H, 4.32. Found: C, 66.18; H, 4.29.

7-Acetyl-4-phenylbenzothiophene (5): mp 114-115.7 °C (hexane/ethyl acetate); IR (KBr) 1666 cm^{-1} (ketone); ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J = 5.7 Hz, 1H), 7.63 (d, J = 5.7 Hz, 1H), 7.60-7.45 (m, 7H), 2.79 (s, 3H); Anal. Calcd. for $C_{16}H_{12}OS$ (252.33): C, 76.16; H, 4.79. Found: C, 76.20; H, 4.91.

7-Ethoxycarbonyl-4-(4-chlorophenyl)benzothiophene (6) : mp 103.1-103.7 °C (hexanes); IR (KBr) 1703 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 8.18 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 5.7 Hz, 1H), 7.53-7.46 (m, 4H), 7.42 (d, J = 5.7 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 4.55-4.48 (q, 2H), 1.48 (t, 3H); Anal. Calcd. for $C_{17}H_{13}ClO_2S$ (316.80): C, 64.45; H, 4.14. Found: C, 64.37; H, 4.49.

6,7-Bis(methoxycarbonyl)-4-(4-chlorophenyl)benzothiophene (7): mp 105.7-107.2 °C; IR (KBr) 1730, 1713 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 7.68 (d, J = 5.7 Hz, 1H), 7.63 (s, 1H), 7.54-7.45 (m, 4H), 7.44 (d, J = 5.7 Hz, 1H), 4.03 (s, 3H), 3.95 (s, 3H); Anal. Calcd. for $C_{18}H_{13}ClO_4S$ (360.81): C, 59.92; H, 3.63. Found: C, 59.65; H, 3.54.

7-Acetyl-4-(4-chlorophenyl)benzothiophene (8): mp 135.4-136.1 °C; IR (KBr) 1666 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 8.08 (d, J = 7.7 Hz, 1H), 7.66 (d, J = 5.7 Hz, 1H), 7.54-7.46 (m, 4H), 7.44 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 5.7 Hz, 1H), 2.8 (s, 3H). Anal. Calcd. for $C_{16}H_{11}ClOS$ (286.78): C, 67.01, H, 3.87. Found: C, 67.13, H, 3.83.

6,7-Bis(benzoyl)-4-(4-chlorophenyl)benzothiophene (9) : foam; IR (KBr) 1657 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 5.7 Hz, 1H), 7.65 (s, 1H), 7.61-7.46 (m, 11H), 7.48-7.28 (m, 4H); mass spectrum *m/e* 452 (M^+).

7-Ethoxycarbonyl-(4-fluorophenyl)benzothiophene (10): mp 110.5-110.8 °C(ethyl acetate/hexane); IR (KBr) 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (d, 1H, J = 7.7 Hz), 7.58 (d, J = 8.2, 1H), 7.55 (m, 2H), 7.43 (d, J = 8.1 Hz, 1H), 7.40 (d, J =

7.7 Hz, 1H), 7.19 (t, 2H), 4.55-4.48 (q, 2H), 1.48 (t, 3H); Anal. Calcd. for $C_{17}H_{13}FO_2S$ (300.35): C, 67.98, H, 4.36. Found: C, 67.90, 4.30.

6,7-Bis(methoxycarbonyl)benzothiophene (11): To an ice-cooled solution of **1** (0.3g, 2.0 mmol) in methanol (20 mL) was added sodium borohydride (0.2 g, 5.2 mmol) and stirred for 0.5h. The solvent was removed on a rotary evaporator and the residue was diluted with ethyl acetate. The ethyl acetate solution was washed with water, brine, dried (Na_2SO_4) and concentrated. To the residue was added dimethyl acetylenedicarboxylate (0.4g, 4.2 mmol), p-toluenesulfonic acid (0.02g) and toluene (5 mL) and the mixture was heated at reflux temperature for 24 hours. The reaction mixture was cooled and purified by flash chromatography (10 % acetone/hexane): oil (0.2g, 40%); IR (KBr) 1722 cm^{-1} (ester): ^1H NMR ($CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 5.5 Hz, 1H), 7.40 (d, J = 5.6 Hz, 1H), 4.01 (s, 3H), 3.94 (s, 3H); mass spectrum *m/e* 250 (M^+).

References and Notes

1. Alder, K.: Rickert, H. F. *Liebigs Ann.*, **1936,** *524*, 180.

2. Patterson, J. W. *J. Org. Chem.*, **1995**, *60*, 560 and references therein.

3. Rajappa, S. *J. Comprehensive Heterocyclic Chemistry*; Ed.; Pergamon Press: New York, 1984, vol.4, p741.

4. Engel, J; Poepen, G. in Houben-Weyl..*Methoden Der Organischen Chemie*, Hetarene I, Teil 2a, Vol. E6b1, Thieme Verlag Stuggart, **1994,** 217.

5. For reviews on indoles see (a) Dopp, D.; Langer, U.; Gerding, B. in Houben-Weyl., *Methoden Der Organishen Chemie,* Hetarene I, Part 2a, Vol. E6b$_1$, G. Thieme Verlag. Stuggart., **1994,** 546-848. (b) ibid. Part 2b, Vol. E6b$_2$. (c) Gribble, G. W., *Contemp. Org. Synthesis,* **1994**, *1*, 145.

6. For reviews on benzofurans see: Röhrkasten, R., Konrad, M. in Houben-Weyl., *Methoden Der Organischen Chemie*, Hetarene I, Teil 2a, vol. E6b1, G. Thieme Verlag. Stuggart, **1994,** 33-162.

7. Kloetzel, M. C.; Little, J. E. Jr.; Frisch, D. M. *J. Org. Chem.* **1953**, *18*, 1511.

8. (a) Davies, W.; Porter, Q. N. *J. Chem. Soc.* **1957,** 4958. (b) Scully, J. F.; Brown, E. V. *J. Am. Chem. Soc.* **1953,** *75,* 6329.

9. (a) Musmar, M. J.; Martin, G. E.; Gampe, R. T.; Lynch, V. M.; Simonsen, S. H.; Lee, M. L.; Tedjamulia, M. L.; Castle, R. N. *J. Heterocycl. Chem.,* **1985,** *22*, 545. (b) Leznoff, C. C., Wolfgang, L., Manning, C. *Can. J. Chem.* **1974,** *52*, 132.

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