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SYNTHESIS OF 2-SUBSTITUTED 3-(2-BENZO[b]THIENYL)- OR 3-(2-THIENYL)-3-METHYLTHIOACRYLONITRILES

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Abstract - Reaction of methyl benzo[b]thiophene-2-dithiocarboxylate(2) with active methylene compounds (malononitrile, methyl cyanoacetate and cyanoacetamide) in the presence of sodium hydride followed by methylation with dimethyl sulfate gave the corresponding 2-substituted 3-(2-benzo[b]thienyl)-3-methylthioacrylonitriles (2-CN, 2-$COOCH_3$, and 2-$CONH_2$)(3a, b, c) in good yields. Compounds 3a and 3b were alternatively synthesized by the reaction of 2-lithiobenzo[b]thiophene with ketenethioacetal [bis(methylthio)methylenemalononitrile and methyl bis(methylthio)-methylenecyanoacetate]. Similarly, 2-cyano-3-methylthio-3-(2-thienyl)acrylonitrile (6) was also prepared from methyl thiophene-2-dithiocarboxylate(5). Methyl dithiocarboxylates (2 and 5) were prepared by the reaction of 2-lithio derivatives of 1 and 4 with carbon disulfide followed by methylation with dimethyl sulfate in good yields.

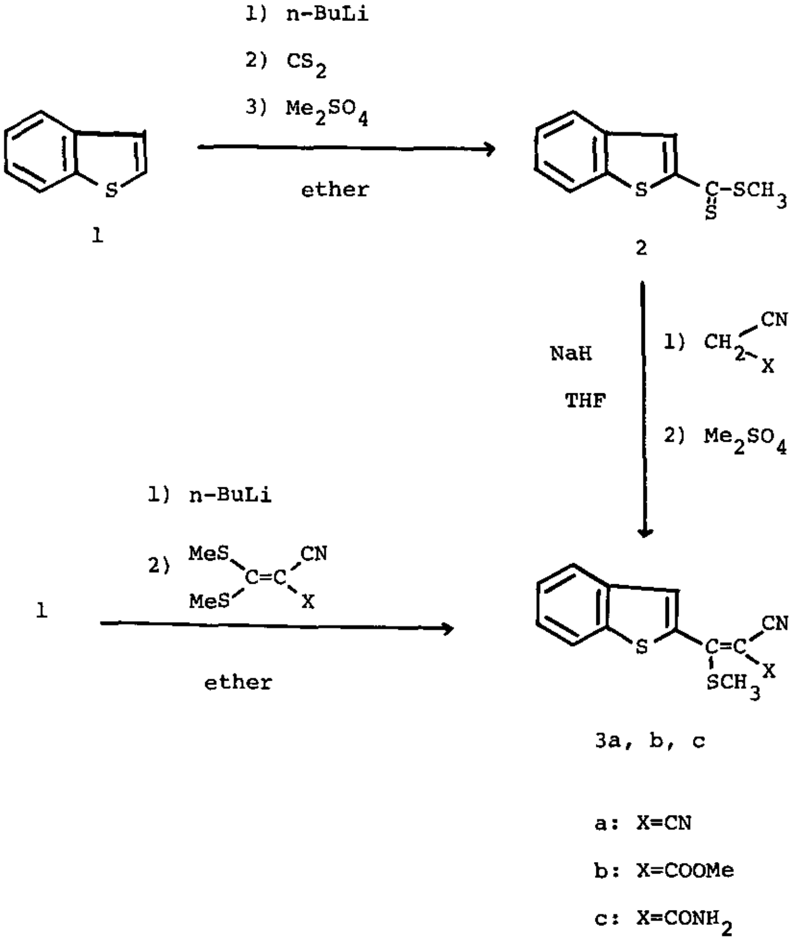
3-Substituted 3-methylthioacrylonitrile derivatives, which are a replacement product of methylthio group in ketenthioacetal, will become to be very useful reagents for the synthesis of heterocyclic compounds. We have reported the synthesis of 2-cyano-3-(3-indolyl)-3-methylthioacrylonitrile using Grignard reaction and the reaction of their products with the nucleophiles such as amines or active methylene compounds.$^{1)}$

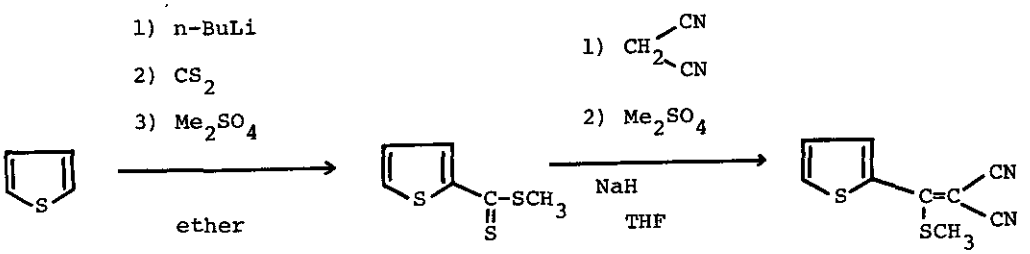
We now wish to report the synthesis of 2-substituted 3-(2-benzo[b]thienyl) or 3-(2-thienyl)-3-methylthioacrylonitriles using the reaction of the 2-lithio compounds with carbon disulfide or ketenethioacetals. It is well known that 2-lithiobenzo[b]thiophene and 2-lithiothiophene are allowed to react with various electrophiles to give the corresponding 2-substituted benzo[b]thiophene and thiophene derivatives in good results.$^{2)}$ This method is adapted for the synthesis of the title compounds.

Condensation of methyl benzo[b]thiophene-2-dithiocarboxylate(2) with malononitrile in the presence of sodium hydride in tetrahydrofuran followed by the methylation with dimethyl sulfate gave 2-cyano-3-(2-benzo[b]thienyl)-3-methylthioacrylonitrile(3a), mp 105-107°C, in 60% yield. [IRν(KBr)cm^{-1}: 2200(C≡N). UVλ_{max}^{EtOH}nm(log ε): 224(4.77), 270(4.40), 346(4.16). NMR(CCl_4)δ : 2.73(3H, s, $S-CH_3$), 7.20-7.70(4H, m, 4, 5, 6, 7-H), 7.83(1H, s, 3-H)]

Similarly, compound 2 also reacted with methyl cyanoacetate or cyanoacetamide to yield the corresponding 2-substituted 3-(2-benzo[b]thienyl)-3-methylthioacrylonitriles(3b: X=COOMe, 3c: X=$CONH_2$) in 70 and 75% yields, respectively. [3b: mp 135-137°C. IRν(KBr) cm^{-1}: 2200(C≡N), 1710(C=O). UVλ_{max}^{EtOH}nm(log ε): 228 (3.51), 262(4.32), 268(4.32), 328(4.13). NMR($CDCl_3$)δ : 2.17(3H, s, $S-CH_3$), 3.90 (3H, s, $O-CH_3$), 7.27(1H, s, 3-H), 7.30-7.50(2H, m, 4, 7-H), 7.70-7.93(2H, m, 5, 6-H). 3c: mp 196-198°C. IRν(KBr) cm^{-1}: 3300, 3360(NH_2), 1640, 1680(C=O), 2200(C≡N). UVλ_{max}^{EtOH}nm(log ε): 228(3.74), 262(4.35), 268(4.35), 324(4.24). NMR(DMSO-D_6)δ : 2.10(3H, s, $S-CH_3$), 7.10-7.27(2H, m, 4, 7-H), 7.30(1H, s, 3-H), 7.80-8.10(2H, m, 5, 6-H)]. 2-Cyano-3-methylthio-3-(2-thienyl)acrylonitrile(6) was also synthesized from methyl thiophene-2-dithiocarboxylate(5) and malononitrile in a manner similar to the preparation of 3a from 2. [6: mp 100-102°C. yield, 60%. IRν(KBr)cm^{-1}: 2200 (C≡N). UVλ_{max}^{EtOH}nm(log ε): 222(4.11), 348(3.81). NMR($CDCl_3$)δ : 2.60(3H, s, $S-CH_3$), 7.23(1H, dd, J=4, 5Hz, 4-H), 7.68(1H, dd, J=1, 4Hz, 3-H), 7.77(1H, dd, J=1, 5Hz, 5-H). Compound 2 was prepared by the condensation of 2-lithiobenzo[b]thiophene, which was prepared by the usual method using n-butyllithium in ether with carbon disulfide, followed by the methylation with dimethyl sulfate, in 85% yield.

Similarly, methyl thiophene-2-dithiocarboxylate(5) was also synthesized from 2-lithiothiophene, carbon disulfide, and dimethyl sulfate in 65% yield. [5: oil[3]. IRν(KBr)cm^{-1}: 1180(C=S). NMR(CCl_4)δ : 2.70(3H, s, S-CH_3), 6.96(1H, dd, J=4, 5Hz, 4-H), 7.47(1H, dd, J=1, 5Hz, 5-H), 7.69(1H, dd, J=1, 4Hz, 3-H)]. Compound 3a and 3b were alternatively prepared by the following unequivocal synthesis. Namely, reaction of 2-lithiobenzo[b]thiophene with bis(methylthio)-methylenemalononitrile or methyl bis(methylthio)methylenecyanoacetate in ether afforded the corresponding 3a and 3b in 48 and 38% yields, respectively. However, when 2-lithiothiophene reacted with bis(methylthio)methylenemalononitrile under the same condition as the case of synthesis of 3a, the desired compound 6 was not isolated as a pure compound from dark brown product.





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REFERENCES AND NOTE

1) G.Kobayashi, S.Furukawa, Y.Matsuda, and Y.Washida, *Chem.Pharm.Bull.*, **15**, 1871 (1967).

2) a) D.A.Shirley and M.D.Cameron, *J.Am.Chem.Soc.*, **74**, 664(1952).
   b) G.M.Brooke and R.King, *Tetrahedron*, **30**, 857(1974).
   c) N.Gjϕs and S.Gronowitz, *Acta.Chem.Scand.*, **25**, 2596(1971).

3) J.Fabian, S.Scheithauer, and R.Mayer, *J.Prakt.Chem.*, **311**, 45(1969).

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