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A FACILE PREPARATION OF 2- AND 5-SUBSTITUTED 3-BROMOTHIOPHENES

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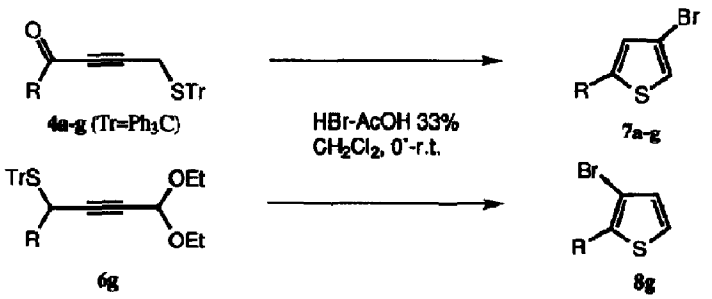
Abstract: Acetylenic ketones of type **4** and acetylenic acetals of type **6** (*Scheme 1*) are excellent cyclization precursors for the acid-catalyzed synthesis of various heterocycles. Using this methodology, 5- and 2-substituted 3-bromothiophenes of types **7** and **8** have been prepared in good to excellent yields.

Thiophene and its derivatives are of great importance in organic chemistry and have found many applications in the pharmaceutical field. Thiophene oligomers have unique electroconductive properties and various substituted thiophenes have been synthesized for this purpose, especially in the search of new superconductors [1]. In the past, the preparation of the thiophene ring system was one of the main interest within the chemistry of five-membered ring heterocycles. Preparation of thiophenes was accomplished using both classical and nonclassical approaches, such as for example: *a*) the general *Hinsberg synthesis* from α-diketones [2], *b*) the standard *Gewald type synthesis* [3], *c*) the *Dieckmann condensation* of mercapto ketone derivatives with alkynes [4], *d*) the *Socony vacuum process* [5], and *e*) electrocyclic reactions [6].

Recently, we described the preparation of substituted 3-halofurans [7] and substituted 3-bromopyrroles [8]. We present in this paper a general synthesis of 5- and 2-substituted 3-bromothiophenes of types **7** and **8** by acid-catalyzed cyclization of the corresponding acetylenic ketones of type **4** and acetylenic acetals of type **6** (*Scheme 1*).

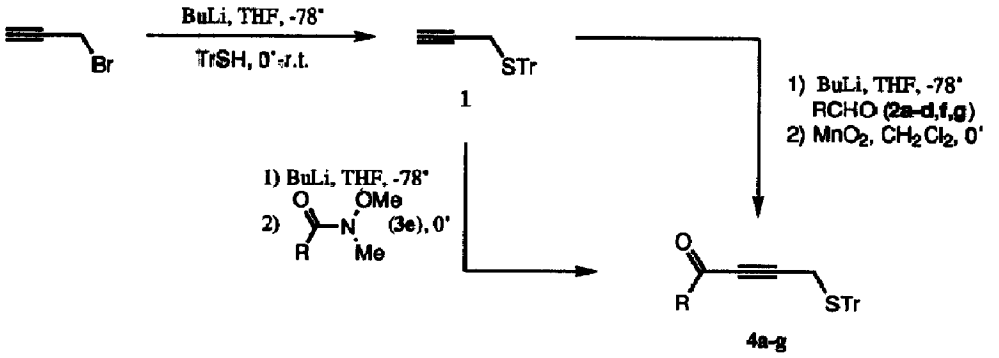
Scheme 1



a: R = 2-furyl ; b: R = 3-furyl ; c: R = 2-thienyl ; d: R = 3-thienyl
e: R = *t*Bu ; f: R = 3,4,5-$(MeO)_3C_6H_2$; g: R = C_8H_{17}

The acetylenic ketones of type **4** were conveniently prepared in good yields by two different ways (*Scheme 2*).

Scheme 2



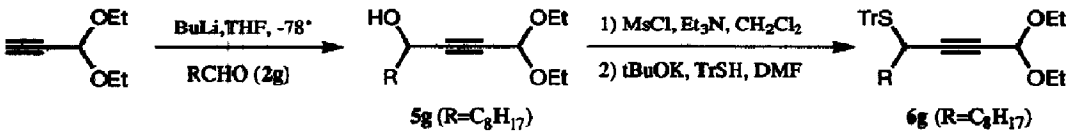
The 2-propynyl trityl sulfide **1** [9] was easily obtained starting from propargyl bromide and triphenylmethanethiol in THF as shown in *Scheme 2*. Treatment of **1** with BuLi at -78°, followed by addition of the corresponding aldehyde **2** and oxidation of the intermediate alcohols with MnO_2 in CH_2Cl_2 afforded the acetylenic ketones **4a-d, f, g** [10] in good overall yields (*Table 1, Method A* [11]). As an alternative method, we used the reaction of the lithium acetylide of **1** (generated in situ from **1** and BuLi in THF) with the *N*-methoxy-*N*-methylamide of type **3** [12] to conveniently prepare the corresponding acetylenic ketones **4** (*Table 1, Method B* [11]).

Table 1 : *Synthesis of Acetylenic the Ketones* ***4a-g.***

	R	Method	Product	Yield [%]
2a	2-furyl	A	**4a**	76
2b	3-furyl	A	**4b**	70
2c	2-thienyl	A	**4c**	80.5
2d	3-thienyl	A	**4d**	75
3e	tBu	B	**4e**	73.5
2f	$3,4,5\text{-}(MeO)_3C_6H_2$	A	**4f**	83
2g	C_8H_{17}	A	**4g**	81.5

The synthesis of the acetylenic acetal **6** was achieved in high yield using the following procedure (*Scheme 3*).

Scheme 3



Treatment of the commercially available 3,3-diethoxyprop-1-yne with BuLi in THF at -78°, followed by addition of aldehyde **2g** afforded the acetylenic alcohol **5g** in 82% yield [7, 13]. Addition of methanesulfonyl chloride in the presence of triethylamine gave the corresponding mesylate and subsequent treatment with tBuOK and triphenylmethanethiol in DMF at r.t. provided the acetylenic

acetal **6g** in 92% isolated yield (*Method C* [11]).The synthesis of the 3-bromothiophenes of types **7** [14] and **8** [15] (*Scheme 1*) was achieved in good yields by treatment of the acetylenic ketones **4a-g** and the acetylenic acetal **6g**, with 33% HBr/AcOH in CH_2Cl_2 (*Method D* [11], *Table 2*) [16].

Table 2 : *Synthesis of 5- and 2-substituted 3-bromothiophenes 7 and 8.*

	R	Method	Product	Yield [%]
4a	2-furyl	D	**7a**	71.5
4b	3-furyl	D	**7b**	67.0
4c	2-thienyl	D	**7c**	90.0
4d	3-thienyl	D	**7d**	82.5
4e	tBu	D	**7e**	82.5
4f	$3,4,5\text{-}(MeO)_3C_6H_2$	D	**7f**	96
4g	C_8H_{17}	D	**7g**	91.0
6g	C_8H_{17}	D	**8g**	81.5

The presented strategy allows us to synthesize regioselectively the isomeric 5- and 2-substitued 3-bromothiophenes **7** and **8** as shown in *Scheme 1*. This approach features triphenylmethanthiol as a useful source for masked sulfur and the trityl group as an efficient protecting group for the synthesis of **4** and **6**, which can be quantitatively cleaved under the cyclization conditions. Since 3-bromothiophenes can be easily substituted in various ways, our approach constitutes a novel and efficient synthesis to highly substituted thiophenes. Applications towards the synthesis of biologically interesting thiophenes using this strategy will be reported in due course.

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9. As an alternative approach, we prepared in analogy to **1** (*Scheme 2*) *tert*-Butyl prop-2-ynyl sulfide **9** as a synthetic equivalent of **1**, starting from 2-Methyl-2-propanthiol and propargyl bromide. **9** allowed us to synthesize the corresponding acetylenic ketones **4** and the acetylenic acetals of **6** in high yields, which smoothly cyclized to the 3-bromothiophenes **7** and **8**. Due to the foul stench of **9** and its derivatives, we focussed primarily on the development of **1**.
10. **4a** : M.p. 111-112°. IR (KBr) : 3432m, 3152w, 3083w, 3025w, 2211m, 1640s, 1490w, 1486m, 769s, 743s, 701s. ^{1}H-NMR ((D_6)DMSO, 250 MHz) : 8.15-8.10 (m, 1 fur. H); 7.40-7.15 (m, 15

arom. H/1 fur. H); 6.80-6.75 (m, 1 fur. H); 3.27 (s, 2 aliph. H). MS : 408 (M^+, <1), 244 (26), 243 (100), 241 (14), 239 (10), 166 (14), 165 (50). Anal. calc. for $C_{27}H_{20}O_2S$ (408.515) : C 79.38, H 4.93, S 7.85 ; found : C79.11, H 4.80, S 7.69.

11. **General Procedures** : *Method A* : To a stirred soln. of 3.15g (10.0 mmol) of 2-propynyl trityl sulfide **1** in absolute THF (30ml) was added under Ar at -78°, 6.6ml (1.05eq.) of BuLi-soln. (1.6M in hexane). The reaction mixture was stirred for 30 min at -78°, followed by addition of 10 mmol of freshly distilled (or recrystallized) aldehyde **2**. After 30 min stirring at -78°, the reaction mixture was slowly brought to 0°, poured onto ice, 1N aq. NaH_2PO_4-soln. and AcOEt. The aq. layer was extracted with AcOEt, the combined org. fractions were dried and the solvents evaporated. The crude residue was dissolved in CH_2Cl_2 (20ml) and slowly added to a mechanically stirred suspension of 26.0g (30eq.) of MnO_2 at 0°. The reaction mixture was stirred for 30 min at 0°, filtered through a plug of $MgSO_4$ and evaporated. The residue was chromatographed on SiO_2 with Et_2O/hexane to yield the substituted acetylenic ketones **4**. *Method B* : To a stirred soln. of 3.15g (10.0 mmol) of 2-propynyl-trityl sulfide **1** in absolute THF (30ml) was added under Ar at -78°, 6.6ml (1.05eq.) of BuLi-soln. (1.6M in hexane). The reaction mixture was stirred for 30 min at -78°, brought to -20°, followed by addition of a soln. of 10 mmol of the *N*-methoxy-*N*-methylamide **3**. The reaction mixture was stirred for 1 hr at 0°, poured onto ice, 1N aq. NaH_2PO_4-soln. and AcOEt. The combined org. fractions were washed with brine, dried, the solvents were evaporated and the residue was chromatographed on SiO_2 with Et_2O/hexane to yield the substituted acetylenic ketones **4**. *Method C* : To a stirred soln. of 10 mmol of acetylenic alcohol **5** in CH_2Cl_2 (30ml) was added under Ar, 1.67ml (12.0 mmol) of Et_3N and 0.94ml (12.0 mmol) of MsCl at 0°. The reaction mixture was stirred for 1 hr at 0°, poured onto ice, 1N aq. NaH_2PO_4-soln. and Et_2O. The combined org. fractions were washed with brine, dried and the solvents were evaporated. The residue was dissolved in DMF (10ml) and added to a stirred mixture of 3.59g (13.0 mmol) of triphenylmethanethiol (*Fluka*) and 1.46g (13.0 mmol) of *t*BuOK in DMF (30ml) at 0°. The reaction mixture was stirred for 1 hr at r.t., poured onto ice, 1N aq. NaH_2PO_4-soln. and AcOEt. The combined org. fractions were washed with brine, dried and the solvents were evaporated. The residue was chromatographed on SiO_2 with Et_2O/hexane (1:20) to yield the substituted acetylenic acetals **6**. *Method D* : To a stirred soln. of 10.0 mmol of the substituted acetylenic derivatives of types **4** and **6** in CH_2Cl_2 (30ml) was added at 0°, 5.0ml of HBr-soln. (33% in AcOH). The reaction mixture was stirred for 2 hr at 0°, poured onto ice, sat. aq. $NaHCO_3$-soln. and Et_2O. The combined org. fractions were washed with brine, dried and the solvents were evaporated. The residue was chromatographed on SiO_2 with mixtures of Et_2O/hexane and distilled or recrystallized, to yield the substituted 3-bromothiophenes of types **7** and **8**.
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14. **7d** : M.p. 69-70°. IR (KBr) : 3439m, 3086w, 1503m, 1378m, 1193m, 824m, 777s. ^{1}H-NMR ((D_6)DMSO, 250 MHz) : 7.85-7.80 (dd, J=3/1.5, 1 thioph. H); 7.70-7.60 (dd, J=5/3, 1 thioph.); 7.58 (d, J=1.5, 1 thioph. H); 7.50-7.40 (m, 2 thioph. H). MS : 246 (100), 244 (92), 165 (34), 127 (20), 121 (86), 89 (10), 82 (20), 69 (18), 63 (10), 45 (28), . Anal. calc. for $C_8H_5S_2Br$ (245.152) : C 39.20, H 2.06, S 26.16 ; found : C39.32, H 2.16, S 25.91.
15. **8g** : B.p. 180°/0.1mbar. IR (Film) : 3150w, 3085w, 2935s, 2854s, 1520w, 1463w, 1437w, 1375w, 1345w, 1152w, 866w, 696m. ^{1}H-NMR ($(D_3)CDCl_3$, 250 MHz)) : 7.10 ; 6.89 (2d, J=5.3, 2 arom. H); 2.85-2.70 (m, 10 aliph. H); 0.88 (t, J=5.9, 3 aliph. H). MS : 408 (M^+, <1), 244 926), 243 (100), 241 (14), 239 (10), 166 (14), 165 (50). Anal. calc. for $C_{12}H_{19}SBr$ (275.25) : C 52.36, H 6.96, S 11.65 ; found : C 52 18, H 7.10, S 11.84.
16. The 3-bromothiophenes should be stored in the freezer and protected from light. They are best used immediately after their preparation for further transformations.

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