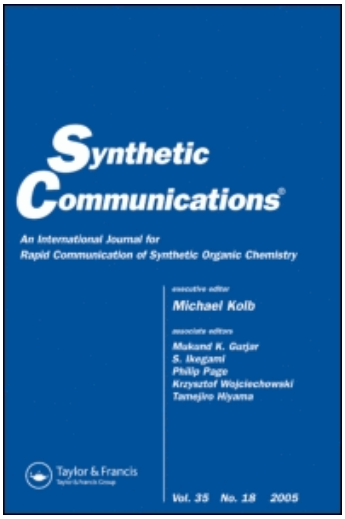


Synthetic Communications
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597304

Direct Synthesis of 2-(Cycloalkylamino)-3,4-Substituted Thiophenes via Selective Deprotonation-Cyclization of Aroyl Ketene N,S-Acetals

Kethiri R. Reddy[a]; Mandava V. Basaveswara Rao[a]; Hiriyakkanavar Ila[ab]; Hiriyakkanavar Junjappa[a]
[a] Department Chemistry, North-Eastern Hill University, Shillong, Meghalaya, India [b] Department of Chemistry, I I T, Kanpur, India

To cite this Article Reddy, Kethiri R. , Rao, Mandava V. Basaveswara , Ila, Hiriyakkanavar and Junjappa, Hiriyakkanavar(1996) 'Direct Synthesis of 2-(Cycloalkylamino)-3,4-Substituted Thiophenes via Selective Deprotonation-Cyclization of Aroyl Ketene N,S-Acetals', Synthetic Communications, 26: 22, 4157 — 4164
To link to this Article: DOI: 10.1080/00397919608004653
URL: http://dx.doi.org/10.1080/00397919608004653

SYNTHETIC COMMUNICATIONS, 26(22), 4157-4164 (1996)

DIRECT SYNTHESIS OF 2-(CYCLOALKYLAMINO)-3,4-SUBSTITUTED THIOPHENES VIA SELECTIVE DEPROTONATION - CYCLIZATION OF AROYL KETENE N,S-ACETALS

Kethiri R. Reddy, Mandava V. Basaveswara Rao,
Hiriyakkanavar Ila*@ and Hiriyakkanavar Junjappa*

Department Chemistry, North-Eastern Hill University
Shillong 793003, Meghalaya, India

***ABSTRACT** : Acyclic and cyclic aroyl ketene N,S-acetals undergo regioselective deprotonation - cyclization via dipole stabilized carbanion in the presence of LDA/THF to afford the corresponding 2-(cycloalkylamino)-4-aryl or 3,4-annelated thiophenes in moderate to good yields.*

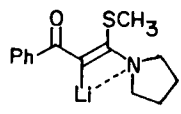
We have recently[1] reported a novel route to 2-alkylthio and 2-alkoxy thiophenes by Simmons-Smith reaction on α-oxoketene S,S- and O,S-acetals respectively[1-3]. A probable mechanism involving insertion of methylene carbenoid into methylthio group to give sulfonium ylid and its subsequent intramolecular Aldol condensation was suggested for the formation of these thiophenes. When the corresponding N,S-acetal **1a** was subjected to Simmons-Smith reaction with a view to extending this approach for the synthesis of 2-N(cycloalkylamino)-thiophenes,the reaction mixture yielded only an

*To whom correspondence should be addressed.

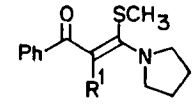
*@Present address : Department of Chemistry, I I T,Kanpur 208 016, India.

intractable tar. The α-oxoketene dithioacetals are known to undergo deprotonation-cyclization in the presence of LDA (THF at -78°C) to yield the corresponding 2-methylthio-thiophenes in moderate yields[4]. Following similar approach, when **1** were deprotonated under identical conditions, the corresponding 2-aminothiophenes **3** were obtained in moderate to good yields. We report herein the results of these studies.

Deprotonation of **1a** was studied under variety of conditions using LDA or LHMDS as bases (LDA/HMPA/THF, LDA/TMEDA/THF, LDA/THF, LHMDS/HMPA/THF,LHMDS/THF etc.). Quenching of the reaction mixture with either D_2O or methyl iodide yielded none of the α-deuterated **5a** or methylated **5b** thus showing the absence of involvement by α-keto vinyllithium

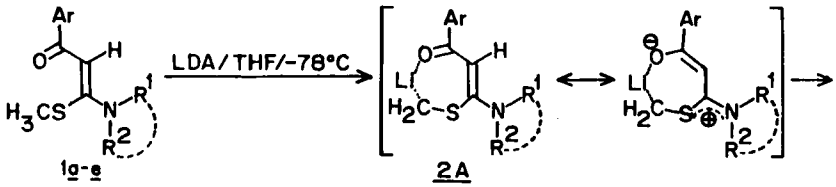


4

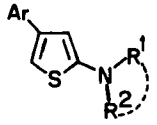


5a, R = D
b, R = CH_3

species **4** through vinylic deprotonation. However in all these reactions, the 2-pyrrolidino-4-phenylthiophene **3a** was obtained in varying yields indicating that kinetic site of deprotonation in **1a** was S-methyl group *cis* to carbonyl oxygen. Best results were obtained when **1a** was treated with LDA/THF at -78°C to afford the thiophene **3a** in 55% yield. The other aroyl ketene N,S-acetals **1b-e** similarly yielded the corresponding 2-amino-4-arylthiophenes **3b-e** in 48-69% overall yields (Scheme 1). All these reactions yielded significant amount of starting materials, while the use of two equivalent of LDA had no effect on the yields of thiophenes. The N,S-acetals **1f** and **1g** derived from tetralone also underwent selective deprotonation and cyclization under identical conditions to give the corresponding 3,4-annelated thiophenes **3f** and **3g** in 52% and 71% yields respectively along with the starting material (Scheme 2). Competetive allylic deprotonation to give the allylic



1a-e

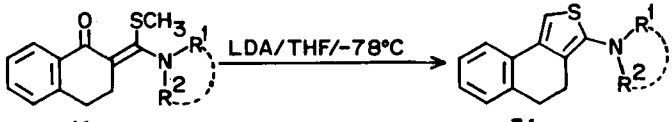


3a-e

1-3	Ar	R^1	R^2	% yield
a	C_6H_5	$-(CH_2)_4-$		55(75)
b	4-$MeOC_6H_4$	$-(CH_2)_4-$		69(73)
c	C_6H_5	$-(CH_2)_5-$		52(68)
d	C_6H_5	$-(CH_2)_2-O-(CH_2)_2$		52(65)
e	C_6H_5	Et	Et	48(58)

yield in parenthesis are based on recovered starting material

Scheme-1

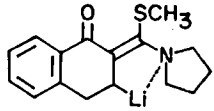


1f-g 3f-g

1, 3f, $R^1 = R^2 = -(CH_2)_4-$ (%) 11
g, $R^1 = R^2 = -(CH_2)_5$ (%) 11

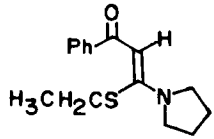
Scheme-2

anion **6** was not operative in these cases as shown by quenching of the reaction mixture with either D_2O or methyl iodide



6

The probable mechanism for the formation of thiophenes **3** from N,S-acetals **1** which is similar to that proposed by Marino and co-workers[5] for 2-methylthio-thiophenes formation from oxoketene dithioacetals is shown in the Scheme 1. Regioselective deprotonation of SCH_3 group in **1** gives dipole stabilized carbanion **2**[6], which could not be trapped by either D_2O or methyl iodide, as it underwent smooth cyclization to thiophenes **3**. It should be noted that S-methyl N,S-acetals are the only derivatives which undergo deprotonation -cyclization to thiophenes **3** since the corresponding S-ethyl analog **7** failed



7

to yield any 5-methyl-2-N(piperidino)-4-phenylthiophene under the stated reaction conditions.

A number of 2-(cycloalkylamino)thiophenes have been synthesized by various methods[7]. The present procedure involving selective deprotonation and cyclization of oxoketene N,S-acetals through dipole stabilized carbanion provides more direct route to this class of thiophenes with new substitution pattern. The enamine reactivity of these newly synthesized thiophenes as potentially useful substrates in cycloaddition reactions is under investigation[7,8].

EXPERIMENTAL

Starting Materials.- The required N,S-acetals **1a-e** were prepared according to the reported procedure by methylation of corresponding thioamides with

methyl iodide in the presence of potassium carbonate in refluxing acetone[9]. All the known N,S-acetals were characterized by comparison of their spectral and analytical data with authentic samples while data for unknown N,S-acetals (**1f**, **1g** and **7**) is given below.

2-Methylthio-2-N(pyrrolidino)methylene-1-tetralone (1f):

Yield 62%, Dark viscous liquid ;IR (neat)γ_{max} 1610, 1039, 1001 cm^{-1}, ^1H NMR (90 MHz, CCl_4); 1.72 (brs, 4H, CH_2); 2.38 (s, 3H, SCH_3); 2.92 (brs, 4H, CH_2); 3.44 (brs, 4H, NCH_2); 7.16-7.32 (m, 3H,ArH); 8.18-8.22 (m,1H, ArH).

Anal. Calcd. for $C_{16}H_{19}NOS$ (273.381): C,70.29; H,7.00; N,5.12. Found: C,70.52; H,7.23; N,5.37.

2-Methylthio-2-N(piperidino)methylene-1-tetralone (1g):

Yield 52%; Dark viscous liquid; IR(neat)γ_{max} 1598, 1041, 1009 cm^{-1}, ^1H NMR (90 MHz, CCl_4); 1.66 (brs, 6H, CH_2); 2.30 (s,3H,SCH_3); 2.86 (brs,4H,CH_2); 3.33 (brs,4H,NCH_2); 7.06-7.43 (m,3H,ArH); 7.96-8.13 (m,1H,ArH).

Anal. Calcd. for $C_{17}H_{21}NOS$ (287.411): C,71.04; H,7.37; N,4.87. Found: C,71.26; H,7.49; N,5.02.

3-Ethylthio-3-N(piperidino)-1-phenyl-2-propen-1-one (7):

Yield 87%; Light yellow liquid; IR(neat) γ_{max} 1610,1496,1456 cm^{-1}; ^1H NMR (90 MHz, $CCl_4/CDCl_3$); 1.29 (t, J=7.5Hz,3H,CH_3); 1.62 (brs,6H,CH_2); 2.83 (q,J=7.5Hz,2H,CH_2); 3.49 (brs, 4H, NCH_2); 5.86 (s,1H,vinylic-H); 7.26-7.51 (m,3H,ArH); 7.76-7.96 (m,2H,ArH).

Anal. Calcd. for $C_{16}H_{21}NOS$ (275.401): C,69.77; H,7.69; N,5.09. Found : C,69.97; H,7.84; N,5.31.

General Procedure for Synthesis of Thiophenes (3a-g):

To a solution of diisopropylamine (1.68 ml, 12 mmol) in sodium dried Tetrahydrofuran (10 ml) under dry argon atmosphere was added 1M solution of n-butyl lithium in ether (7.5 ml, 10 mmol), over 20 min, with stirring and temperature control at 0°C with an ice bath. To the resulting solution of LDA at -78°C, was added α-oxoketene N,S-acetal (7.5 mmol) in THF (25 ml). The mixture was stirred at -78°C for 30 min, and then allowed to warm to

room temperature for 5-6 h (monitored by tlc). The reaction mixture was quenched with sat. aq. NH_4Cl (100 ml), extracted with $CHCl_3$ (3x25 ml). The combined extracts were washed with water (3x25 ml), dried (Na_2SO_4) and evaporated to give a viscous residue which was purified by column chromatography over silica gel using hexane as eluent.

4-Phenyl-2-N(pyrrolidino)thiophene (3a):

Yield 55%; Viscous low melting solid; IR (CCl_4)γ_{max}1539,1509 cm^{-1}; ^1H NMR (90 MHz,CCl_4); 1.85-2.18(m,4H,CH_2); 3.11-3.45(m,4H,NCH_2); 5.99(brs,1H,H-3); 6.49 (brs,1H,H-5); 7.11-7.67(m,5H,ArH).

Anal. Calcd. for $C_{14}H_{15}NS$ (229.331): C,73.32; H,6.59; N,6.11. Found : C,73.54;H,6.72; N,6.29.

4-(4-Methoxyphenyl)-2-N(pyrrolidino)thiophene 3b:

Yield 69%; m.p.105-107°C; IR(KBr) γ_{max}1505,1476,1238 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$); 1.81-2.20 (m,4H,CH_2); 3.02-3.55 (m,4H,NCH_2); 3.63 (s, 3H, CH_3O); 6.00 (brs,1H,H-3); 6.44 (brs,1H,H-5); 6.91 (d,J=8.5Hz,2H,ArH); 7.74 (d,J=8.5Hz,2H,ArH). MS: m/z 259 (M^+,100); 244(15), 216(11), 203(12).

Anal. Calcd. for $C_{15}H_{17}NOS$ (259.361): C,69.46; H, 6.61; N,5.40. Found : C,69.52; H,6.78; N,5.57.

4-Phenyl-2-N(piperidino)thiophene (3c):

Yield 52%; viscous liquid; IR(neat) γ_{max}1490,1442,1210 cm^{-1}; ^1H NMR (90 MHz, CCl_4); 1.43-1.91(brs,6H,CH_2); 3.00-3.29(brs,4H,NCH_2); 6.36 (brs, 1H, H-3); 6.68(brs,1H,H-5); 7.24-7.58(m,5H,ArH). MS: m/z 243 (M^+, 62); 242(26).

Anal. Calcd. for $C_{15}H_{17}NS$ (243.361): C,74.03; H,7.04; N,5.76. Found : C,74.28;H,7.20; N,5.91.

2-N(Morpholino)-4-phenylthiophene (3d):

Yield 52%; viscous liquid; IR(neat) γ_{max}1591,1485,1443,1205 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$); 3.00-3.22 (brt,J=5Hz,4H,NCH_2); 3.68-3.93 (brt,J=5Hz,4H,OCH_2); 6.44 (d,J=1.5Hz,1H,H-3);6.78 (d,J=1.5Hz,1H,H-5); 7.23-7.61(m,5H,ArH); MS: m/z 245 (M^+,100); 187(47); 147(23).

Anal. Calcd. for $C_{14}H_{15}NOS$ (245.331): C,68.54; H,6.16; N,5.71. Found : C,68.72;H,6.30; N,5.91.

2-N(Diethylamino)-4-phenylthiophene (3e):

Yield 48%; viscous liquid; IR(neat) γ_{max}1499,1443,1257 cm^{-1}; ^1H NMR (90 MHz,CCl_4); 1.03 (t,J=7Hz,6H,CH_3); 3.18 (q,J=7Hz,4H,NCH_2); 6.49 (brs,1H, H-3); 6.75 (brs,1H,H-5); 7.20-7.60(m,5H,ArH).

Anal. Calcd. for $C_{14}H_{17}NS$ (231.351): C,72.68; H,7.41; N,6.05. Found: C,72.73;H,7.68;N,6.25.

2-N(Pyrrolidino)-3,4-dihydronaphtho[2,1-c]thiophene (3f):

Yield 52%; Viscous low melting solid; IR(neat) γ_{max}1616,1558,1216cm^{-1}; ^1H NMR (90 MHz/$CDCl_3$); 1.97 (brs,4H,CH_2); 2.85 (brs,4H,CH_2); 3.26 (brs,4H, NCH_2); 6.93 (s,1H,H-5); 7.05-7.57(m,3H,ArH); 7.58-7.83(m,1H,ArH).

Anal. Calcd. for $C_{16}H_{17}NS$ (255.371): C,75.25; H,6.71; N,5.48. Found : C,75.44;H,6.87;N,5.67.

2-N(Piperidino)-3,4-dihydronaphtho[2,1-c]thiophene (3g):

Yield 71%; Viscous low melting solid; IR(neat) γ_{max} 1598,1551,1501,1440cm^{-1}; ^1H NMR (90 MHz, CCl_4); 1.42-1.92(brs,6H,CH_2); 2.53-2.98(m,8H,NCH_2 and CH_2); 6.94 (s,1H,H-4); 7.04-7.36(m,3H,ArH); 7.43-7.63(m,1H,ArH);

MS: m/z 269 (M^+,100), 198(16), 185(57), 173(58).

Anal. Calcd. for $C_{17}H_{19}NS$ (269.391): C,75.79;H,7.11;N,5.20.Found: C, 75.89; H,7.32; N,5.42.

ACKNOWLEDGEMENTS

KRR and MVB thank CSIR and IFCPAR for Research associateship and Senior research fellowship. Financial assistance under CSIR scheme is also acknowledged.

REFERENCES AND NOTES

1. Thomas, A.; Singh, G.; Ila, H. and Junjappa, H. Tetrahedron Lett. **1989**, *30*, 3093.
2. Bhat, L.N.;Thomas, A.; Ila, H. and Junjappa, H. Tetrahedron **1992**,*48*, 10377.

3. Bhat, L.N.; Ila, H. and Junjappa, H. Synthesis **1993**, 959.
4. Marino, J.P. and Kostusyk, J.L. Tetrahedron Lett. **1979**, *27*, 2489.
5. Marino, J.P. and Kostusyk, J.L. Tetrahedron Lett. **1979**, *27*, 2493.
6. Reetz, D.B.; Beak, P.; Farney, R.F. and Helmick, L.S.J.Am.Chem. Soc. **1978**, *100*, 5428.
7. Morris, R.K. in 'Aminothiophenes and Their Derivatives' in "Thiophene and Its Derivatives"; Gronowitz, S., Ed., Chapter V, Part II, Wiley Inter Science, pp. 631-799.
8. Reinhoudt, D.N.; Trompenaars, W.P. and Geevers, J. Synthesis **1978**, *21*, 368 and references therein.
9. Vishwakarma, J.N.; Apparao, S.; Ila, H. and Junjappa, H. Ind. J. Chem. **1985**, *24B*, 466.

(Received in the UK 22 May 1996)