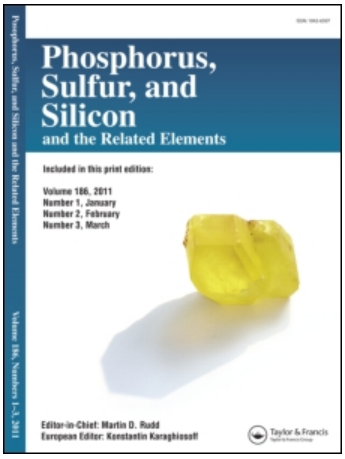


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

STUDIES ON THE ALKYLATION OF β-OXO THIOAMIDES WITH α-BROMOKETONES: SELECTIVE CYCLIZATION OF THE INTERMEDIATE α-OXO KETENE-N, S-ACETALS TO THIOPHENE DERIVATIVES

S. Suma[a]; N. K. Ushakumari[a]; C. V. Asokan[a]
[a] School of Chemical Sciences, Mahatma Gandhi University, Kerala, India

To cite this Article Suma, S. , Ushakumari, N. K. and Asokan, C. V.(1997) 'STUDIES ON THE ALKYLATION OF β-OXO THIOAMIDES WITH α-BROMOKETONES: SELECTIVE CYCLIZATION OF THE INTERMEDIATE α-OXO KETENE-N, S-ACETALS TO THIOPHENE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 131: 1, 161 — 171
To link to this Article: DOI: 10.1080/10426509708031604
URL: http://dx.doi.org/10.1080/10426509708031604

Phosphorus, Sulfur, and Silicon, 1997, Vol. 131, pp. 161–171
Reprints available directly from the publisher
Photocopying permitted by license only

STUDIES ON THE ALKYLATION OF β-OXO THIOAMIDES WITH α-BROMOKETONES: SELECTIVE CYCLIZATION OF THE INTERMEDIATE α-OXO KETENE-N,S-ACETALS TO THIOPHENE DERIVATIVES

S. SUMA, N. K. USHAKUMARI and C. V. ASOKAN*

School of Chemical Sciences, Mahatma Gandhi University, Priyadarshini Hills, Kottayam-686 560, Kerala, India

(Received 29 July 1997; In final form 26 August 1997)

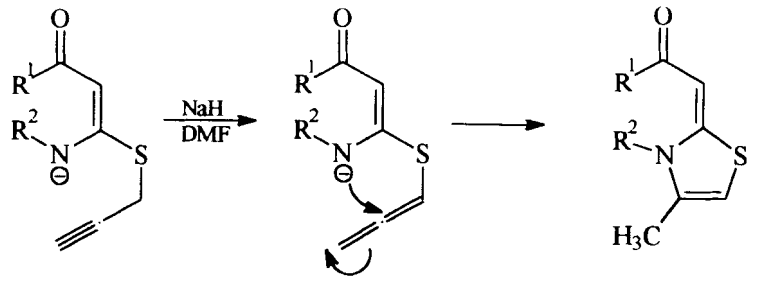
The addition of enolate anions obtained from substituted aryl methyl ketones in the presence of NaH and DMF to phenyl isothiocyanate on subsequent alkylation with phenacyl bromide or α-bromo propiophenone underwent intramolecular cyclization involving the ketene-N,S-acetal moiety and carbonyl group to afford 2-phenylamino-3-aroyl-4-phenyl-5-methyl/unsubstituted thiophenes. Reaction of enolates derived from acetyl acetone and ethyl acetoacetate under similar conditions underwent intramolecular aldol condensation resulting in the formation of substituted thiophenes.

Keywords: Thiophenes; α-Oxo ketene-N,S-acetals; β-Oxo thioamides; Intramolecular cyclization; Isothiocyanates; Thiazoles

INTRODUCTION

The addition of enolates derived from active methylene ketones on aryl or alkyl isothiocyanates afford thiolate anions which on protonation give β-oxo thioamides.[1] The intermediate thiolate anions on alkylation lead to the formation of α-oxo ketene-N,S-acetals.[2] Functionalized ketene-N,S-acetals are versatile intermediates in organic synthesis.[3] Adducts obtained by the reaction of suitably functionalized substrates to isothiocyanates can undergo subsequent intramolecular cyclization to give sulfur containing heterocyclic systems.[4] Alternatively alkylation of the intermediate thiolate anion with 1,2-bielectrophiles such as

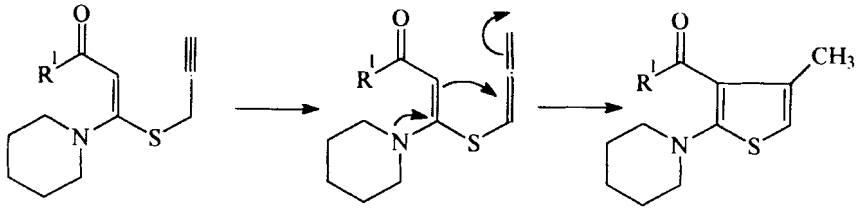
*Corresponding author. E-mail: mgu@md2.vsnl.net.in



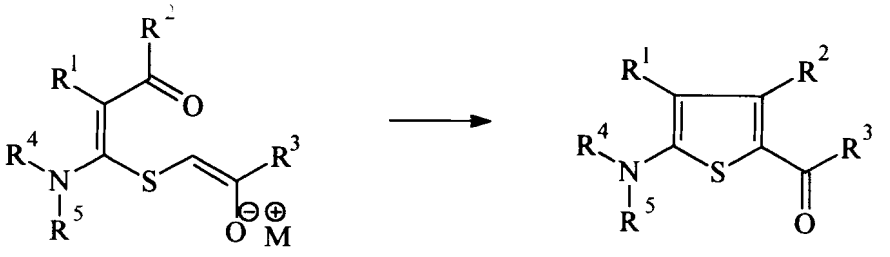
1 2 3

R^1 = Aryl, R^2 = Aryl or Alkyl

α-halo carbonyl compounds or nitriles also lead to the formation of heterocycles usually derivatives of thiophenes or thiazoles.[5] Junjappa *et.al.* have reported the reaction of β-oxo thioamides with propargyl bromide.[6] The β-oxo thioamide, having a secondary amino substituent on alkylation with propargyl bromide afford thiazole derivatives, while similar reaction of tertiary amino substituted thioamides gave functionalized thiophenes. Formation of thiazole involve intramolecular addition of the nitrogen on to the allene obtained by the rearrangement of the propargyl group whereas the formation of thiophene involve an intramolecular addition of the enamine moiety to the allene (Scheme 1 & Scheme 2). In continuation with our studies on the synthetic applications of β-oxo thioamides and α-oxo ketene-N,S-acetals we have examined the reaction of enolates derived from active methylene ketones with phenyl isothiocyanate followed by alkylation with phenacyl bromide in order to understand which mode of cyclization would be preferred.



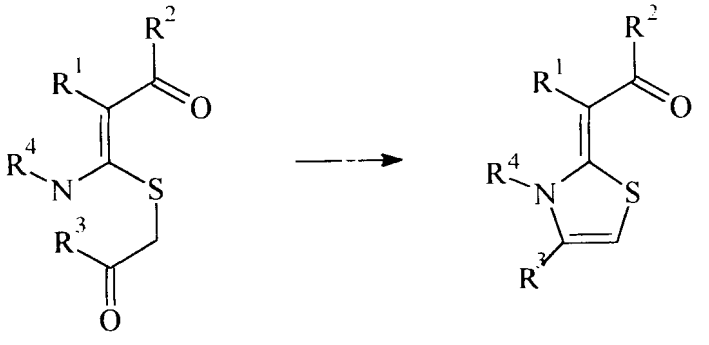
4 5 6



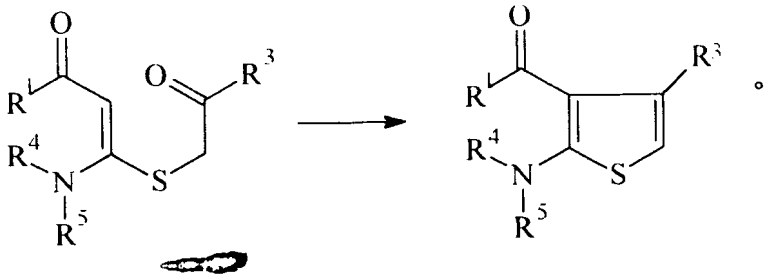
7 8

RESULTS AND DISCUSSION

There are some reports in the literature on the addition of enolates derived from active methylene ketones to aryl or alkyl isothiocyanates followed by alkylation with α-haloketones.[5] Two modes of cyclizations are usually observed. Deprotonation of the methylene group adjacent to the sulfur of the intermediate aryl ketene-N,S-acetal followed by the intramolecular aldol type condensation of the resultant enolate ion **7** leads to the formation of the functionalized thiophene **8** (Scheme 3). Alternatively when the intermediate ketene-N,S-acetal have a secondary amino substituent, intramolecular cyclization involving nucleophilic attack of nitrogen to the carbonyl group β- to the sulfur may lead to the formation of the thiazole derivative **10** as well (Scheme 4). When the α-position of the ketene-N,S-acetal moiety is not substituted, a third mode of cyclization is also possible. This involves the attack of the enamine functionality to the carbonyl group β-to the sulfur atom to form thiophenes **12** (Scheme 5). The examples

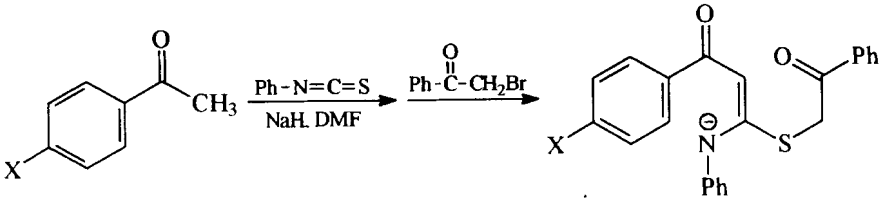


9 10

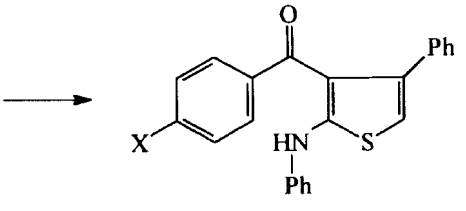


11 **12**

reported in the literature[15a,b,c,7] follow either the first or the second mode of cyclization. The reaction of substituted acetophenones with phenyl isothiocyanate in the presence of NaH as the base followed by alkylation with phenacyl bromide lead to the formation of the intermediate ketene-N,S-acetal **14** (Scheme 6) which in principle can undergo cyclization through any one of the three modes of intramolecular nucleophilic addition to the carbonyl group mentioned above. Our results show that at least in the case of ketene-N,S-acetals **14** cyclization involving the addition of the enamine through the α-carbon to the carbonyl group is the preferred pathway. Thus when acetophenone was allowed to react with one equivalent of phenyl isothiocyanate in DMF in the presence of sodium hydride followed by alkylation with phenacyl bromide, the only product that

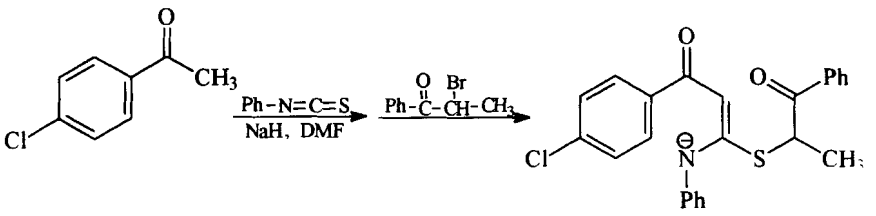


13a-d **14a-d**

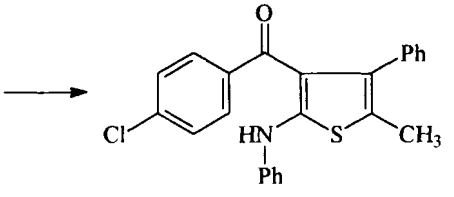


15a-d

13-15	X
a	H
b	Me
c	OMe
d	Cl



16

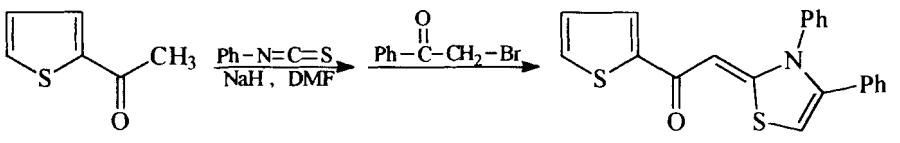


17

could be obtained in pure form by column chromatography was 3-benzoyl-2-phenylamino-4-phenyl thiophene **15a**. The structure of the thiophene **15a** was confirmed with the help of spectral and analytical data. Other substituted acetophenones **13b–d** also exhibited the same pattern of reactivity and functionalized thiophenes **15b–d** were obtained in moderate to good yields. Presence of NH proton in the NMR spectra of the products rules out the direct involvement of nitrogen in cyclization and the formation of thiazole derivatives. Mass spectra of compounds **15a–d** show peaks corresponding to $(Ar\text{-}CO)^{\cdot +}$ which suggests that the carbonyl group α-to the ketene-N,S-acetal moiety is also not involved in the cyclization. Obviously the delocalization of the negative charge on the nitrogen atom should make this carbonyl carbon much less electrophilic.

We have further examined the alkylation of the intermediate thiolate anion, obtained by the addition of substituted acetophenone on phenyl isothiocyanate, by 2-bromopropiophenone. Thus the reaction of *p*-chloroacetophenone with phenyl isothiocyanate in the presence of sodium hydride in DMF followed by alkylation with 1-phenyl-2-bromopropanone gave 3-*p*-chlorobenzoyl-5-methyl-2-phenylamino-4-phenyl thiophene **17**, in 43% yield (Scheme 7). The structure of **17** was confirmed with the help of spectral and analytical data (experimental). This provide further evidence for the confirmation of the structures of **15a–d** as well.

However, the intermediate thiolate anion, obtained by the addition of acetyl thiophene to phenyl isothiocyanate, on alkylation with phenacyl bromide gave the thiazole derivative **19** in 80% yield under similar reaction condition (Scheme 8).

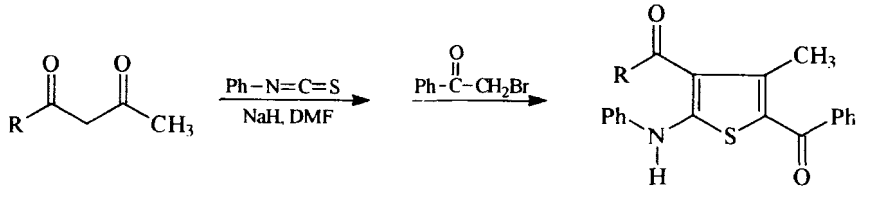


18 **19**

Finally we have examined the reactions of acetyl acetone and ethyl acetoacetate under similar conditions. Here, since the α-position of the intermediate ketene-N,S-acetal is substituted, cyclization involving the enamine functionality is not possible. The products that we have isolated were identified to be the thiophenes **21a** and **21b** (Scheme 9). This suggests that under our reaction conditions, the enolate anion derived from the phenacyl moiety undergo intramolecular addition to the carbonyl group of the acyl group. However in a recent report[7d,8] Mohareb and co-workers have reported the formation of thiazole derivatives on the reaction of 1,3-dicarbonyl compounds such as ethyl acetoacetate, acetyl acetone and ethyl cyanoacetate with phenyl isothiocyanate in the presence of base followed by alkylation with α-haloketones. Alkylation of the thioamides, obtained by the addition of the appropriate enaminoketones to phenyl isothiocyanate, by phenacyl bromide and subsequent cyclization is known to afford thiophenes **21**.[9a,b]

CONCLUSIONS

The α-oxo ketene-N,S-acetals, given by the alkylation of the adducts formed from substituted acetophenones and phenyl isothiocyanate, with α-haloketones such as phenacyl bromide or 2-bromopropiophenone preferably undergo intramolecular cyclization involving the addition of the enamine functionality to the carbonyl group. It is interesting to note that cyclization involving a new carbon



20a, R = CH_3 **21a**, R=CH_3

b, R = OC_2H_5 **b**, R=OC_2H_5

carbon bond formation is preferred to the direct intramolecular addition of the nitrogen to the carbonyl group even if the amino substituent is secondary. When the α-position of the intermediate ketene-N,S-acetal is substituted with an acyl group intramolecular aldol type condensation is preferred to the direct addition of the nitrogen to the carbonyl group, at least under our experimental conditions. The reaction of active methylene ketones with aryl or alkyl isothiocyanate in the presence of base, on subsequent treatment with 1,2-bielectrophiles often provide a useful procedure for the synthesis of highly functionalized thiophenes. Further studies to understand the role of substituents in determining the mode of cyclization are in progress.

EXPERIMENTAL

Melting points were taken on electrically heated block and were uncorrected. The IR spectra were recorded on Shimadzu IR-470 Infrared spectrometer and are reported in cm^{-1}. ^1H NMR spectra were recorded on an EM 390–90 MHz NMR spectrometer in $CDCl_3$ solution with TMS as the internal standard. The Mass Spectra were recorded on a Finnigen-Mat 312 model spectrometer. Commercial solvent dimethyl formamide (DMF) was distilled and dried before use. Sodium hydride (50%) was obtained from Spectrochem, Bombay and was washed with dry petroleum ether before use. Phenyl isothiocyanate[10] and phenacyl bromide[11] were prepared according to the reported methods. Substituted acetophenones, ethyl acetoacetate and acetyl acetone were obtained from Siscochem, Bombay.

3-Aroyl-2-phenylamino-4-phenylthiophenes (15) To an ice cooled and well stirred suspension of sodium hydride (480mg, 10mmol, 50%) in dry DMF (20 mL), sustituted acetophenone **13** (5mmol) was added followed by phenyl isothiocyanate (0.67g, 5mmol) in 5ml DMF. The mixture was stirred at 0–5°C for six hours. Then phenacyl bromide (0.96g, 5mmol) in 5ml DMF was added slowly over half an hour. The reaction mixture was stirred overnight at room temperature and then poured over crushed ice (250g) and extracted with diethyl ether (3 × 50mL). The organic layer was dried over anhydrous sodium sulfate and was evaporated to give a brown viscous residue. The residue was column chromatographed over silicagel (60–120 mesh) using hexane:ethyl acetate (20:1) as eluent to give **15** which were recrystallized from hexane:chloroform mixture (30:1).

3-Benzoyl-2-phenylamino-4-phenylthiophene (15a) was obtained from the reaction of acetophenone with phenylisothiocyanate as an yellow crystalline solid (1.24g, 70% yield) mp 118–119°C; IR (KBr, $\upsilon\, cm^{-1}$) 3430 (broad), 1585,

1595, 1570, 1540, 1255, 745, 735, 700; ^{1}H NMR ($CDCl_3$) δ 6.00 (s, 1H), 6.55–7.35 (m, 15H), 11.50 (s, 1H); EIMS (m/z) 355 (100%, M^+), 322, 277, 262, 105, 77; Anal. Calcd. for $C_{23}H_{17}NOS$ (355.45) C, 77.72; H, 4.82; N, 3.94% Found C, 77.80; H, 4.97; N, 3.85%.

2-Phenylamino-3-(4′-methylbenzoyl)-4-phenyl thiophene (15b) was obtained from the reaction of *p*-methyl acetophenone with phenyl isothiocyanate as an yellow crystalline solid (1.07g, 58% yield); m.p 130–31°C; IR (KBr, υ cm^{-1}) 3430(broad), 1600, 1560, 1540, 255, 760, 745, 735, 700; ^{1}H NMR ($CDCl_3$)δ 2.1 (s, 3H), 6.1 (s, 1H), 6.5–7.4 (m, 14H), 11.2 (s, 1H); EIMS (m/z) 369 (M^+), 336, 119, 262, 91, 77; Anal. Calcd. for $C_{24}H_{19}NOS$ (369.12) C, 78.02; H, 5.19; N, 3.79% Found C, 78.14; H, 5.08; N, 3.70%.

2-Phenylamino-3-(4′-methoxybenzoyl)-4-phenyl thiophene (15c) was obtained from the reaction of *p*-methoxy acetophenone with phenyl isothiocyanate as an yellow crystalline solid (1.05g, 55% yield); m.p 105–06°C; IR (KBr, υ cm^{-1}) 3450(broad), 1600, 1580, 1530, 1255, 745, 735, 700; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H), 6.15–7.50 (m, 15H), 11.2 (s, 1H); EIMS (m/z) 385 (M^+) 355, 256, 223, 106, 112, 77; Anal. Calcd. for $C_{24}H_{19}NO_2S$ (385.11) C, 74.78; H, 4.97; N, 3.64% Found C, 74.65; H, 4.86; N, 3.76%.

2-Phenylamino-3-(4′-chlorobenzoyl)-4-phenyl thiophene (15d) was obtained from the reaction of *p*-chloro acetophenone with phenyl isothiocyanate as an yellow crystalline solid (1.2g, 62% yield); m.p 145–46°C; IR (KBr, υ cm^{-1}) 3430(broad), 1580, 1529, 1490, 255, 755, 725, 695; ^{1}H NMR ($CDCl_3$) δ 6.30 (s, 1H), 6.9 – 7.5 (m, 14H), 11.2 (s, 1H); ^{13}C NMR δ 106.3, 127.5, 129.6, 130.2, 136.9, 138.3, 130.4, 141.5, 162.2, 191.4.; EIMS (m/z) 390 ($M^+ + 1$, 100%) 357, 139, 111, 77.; Anal. Calcd. for $C_{23}H_{16}ClNOS$ (389.46) C, 70.94; H, 4.14; N, 3.60% Found C, 71.06; H, 4.03; N, 3.49%.

3-(4′-Chlorobenzoyl-5-methyl-4-phenyl-2-phenylaminothiophene (17) To an ice cooled and well stirred suspension of sodium hydride (480mg, 10mmol, 50%) in dry DMF (20 mL), *p*-chloroacetophenone (0.77g, 5mmol) was added followed by phenyl isothiocyanate (0.67 g, 5mmol) in 5ml DMF. The mixture was stirred at 0–5°C for six hours. Then the 2-bromopropiophenone (1.13g, 5mmol) in 5ml DMF was added slowly over half an hour. The reaction mixture was stirred overnight at room temperature and then poured over crushed ice (250g) and extracted with diethyl ether (3 × 50mL). The organic layer was dried over anhydrous sodium sulfate and was evaporated to give a brown viscous residue. The residue was column chromatographed over silicagel (60–120 mesh) using hexane:ethyl acetate (20:1) as eluent to give the substituted thiophenes **17** which was recrystallized from hexane:chloroform mixture (30:1) to give an yellow crystalline solid (0.86g, 43%yield); m.p: 128–29°C; IR (KBr, υ cm^{-1}) 1578 1540,(C-Cstr), 1275(C-Nstr) 780, 755, 735, 695(C-Hdef); ^{1}H NMR ($CDCl_3$ δ

ppm) 2.24(s,3H) 6.90–7.60(m, 14H) 11.4(s, 1H); ^{13}C NMR(δ ppm): 135.894, 130.255, 129.808, 128.435, 127.630, 123.662, 119.395. EIMS (m/z) 403 (M^+) 392, 372, 257, 216, 140, 106, 93, 77.; Anal. Calcd. for $C_{24}H_{18}ClNOS$ (403.08) C, 71.45; H, 4.50; N, 3.47% Found C, 71.33; H, 4.66; N, 3.34%.

3,4-Diphenyl-2-(2-thienoyl methylene)-2,3-dihydro-1,3-thiazole (19) To an ice cooled and well stirred suspension of sodium hydride (480mg, 10mmol, 50%) in dry DMF (20 mL), acetylthiophene (0.63g, 5mmol) was added followed by phenyl isothiocyanate (0.67 g, 5mmol) in 5ml DMF. The mixture was stirred at 0–5°C for six hours. Then phenacyl bromide (0.96g, 5mmol) in 5ml DMF was added slowly over half an hour. The reaction mixture was stirred overnight at room temperature and then poured over crushed ice (250g) and extracted with diethyl ether (3 × 50mL). The organic layer was dried over anhydrous sodium sulfate and was evaporated to give a brown viscous residue. The residue was column chromatographed over silicagel (60–120 mesh) using hexane:ethyl acetate (20:1) as eluent to give the substituted thiazole **19** which was recrystallized from hexane:chloroform mixture (30:1) as an yellow solid (1.4g, 80% yield); m.p 128–29°C; IR (KBr, υ cm^{-1}) 3430(broad), 1615, 1580, 1275, 755, 715, 695; ^1H NMR ($CDCl_3$) δ 6.1 – 8.2 (m, 15H Aromatic and vinylic); ^{13}C NMR δ 176.201, 164.774, 146.784, 141.175, 137.565, 130.076, 129.748, 129.151, 129.032, 128.823, 128.614, 128.286, 128.137, 127.928, 127.361, 126.675, 117.695, 106.745, 87.800; EIMS (m/z) 361 (M^+) 328, 250, 215, 111(100%) 105, 77.; Anal. Calcd. for $C_{21}H_{15}NOS_2$ (361.06) C, 69.97; H, 4.19; N, 3.88% Found C, 70.11; H, 4.30; N, 3.74%.

5-Benzoyl-3-ethoxycarbonyl/acetyl-4-methyl-2-phenylaminothiophene (21) To an ice cooled and well stirred suspension of sodium hydride (480mg, 10mmol, 50%) in dry DMF (20 mL), the ketone **20** (5mmol) was added followed by phenyl isothiocyanate (0.67 g, 5mmol) in 5ml DMF. The mixture was stirred at 0–5°C for six hours. Then phenacyl bromide (0.96g, 5mmol) in 5ml DMF was added slowly over half an hour. The reaction mixture was stirred overnight at room temperature and then poured over crushed ice (250g) and extracted with diethyl ether (3 × 50mL). The organic layer was dried over anhydrous sodium sulfate and was evaporated to give a brown viscous residue. The residue was column chromatographed over silicagel (60–120 mesh) using hexane:ethyl acetate (20:1) as eluent to give the substituted thiophenes **21**[9] which were recrystallized from hexane:chloroform mixture (30:1).

5-Benzoyl-3-ethoxycarbonyl-4-methyl-2-phenylaminothiophene (21a) was obtained from the reaction of acetyl acetone with phenyl isothiocyanate as an yellow crystalline solid (1.35g, 74% yield); m.p 169°C; IR (KBr, υ cm^{-1}) 3430(broad), 1635, 1619, 1595, 1240; ^1H NMR ($CDCl_3$) δ 1.45 (d,3H J = 7Hz) 2.4(s,3H) 4.40(q,J = 7Hz) 7.00–8.00(m,10H) 10.7(br-s 1H); ^{13}C NMR δ 4.3,

17.9, 60.5, 120.1, 124.5, 128.1, 128.3, 128.6, 129.6, 131.5; EIMS (m/z) 365 (M^+) 318, 105(100%), 93, 77; Anal. Calcd. for $C_{21}H_{19}NO_3S$ (365.11) C, 69.02; H, 5.24; N, 3.84% Found C, 69.16; H, 5.11; N, 3.69%.

5-Benzoyl-3-acetyl-4-methyl-2-phenylaminothiophene (21b) was obtained from the reaction of ethyl acetoactate with phenyl isothiocyanate as an yellow crystalline solid (1.17g, 70% yield); m.p 172°C; IR (KBr, $\upsilon\,cm^{-1}$) 3430(broad), 1610, 1580, 1538, 490, 1260; ^1H NMR ($CDCl_3$) δ 1.7(br-s, 3H), 2.6(s, 3H), 7.1–7.9(m, 10H), 12.15(br-s, 1H); ^{13}C NMR δ 18.4, 31.4, 50.9, 120.6, 124.9, 127.9, 128.3, 128.5, 129.5, 131.6, 139.4, 144.9, 164.4.; EIMS (m/z): 335M^+, 302, 291, 105, 77; Anal. Calcd. for $C_{20}H_{17}NO_2S$ (335.10) C, 71.62; H, 5.11; N, 4.18% Found C, 71.64; H, 4.97; N, 4.12%.

Acknowledgements

We are indebted to Council of Scientific and Industrial Research, Government of India for financial support (Research project 01(1324)/94). We thank directors of Regional Sophisticated Instrumentation Centers at IIT Madras, NEHU Shillong and CDRI Lucknow for providing spectral data.

References

[1] (a) S. Hüning, K. Hübner and E. Benzing, *Chem. Ber.*, **95**, 926, (1962). (b) R. Bossio, S. Marcaccini, R. Pepino and T. Torroba, *J. Chem. Soc. Perkin* **1**, 229, (1996).

[2] (a) W. D. Rudorf, A. Schierhon and M. Augustine, *Z. Chem.*, **21**, 69, (1981). (b) Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zassihi* **95**, 378, (1975). (c) M. Augustine, W. D. Rudorf and U. Schmidt, *Tetrahedron* **32**, 3055, (1976). (d) W. D. Rudorf and M. Augustine, *Phosphorus Sulfur* **9**, 329, (1981). (e) R. T. Chakrasali, H. Ila and H. Junjappa, *Synthesis* 453, (1988). (f) A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, *Synthesis* 748, (1980).

[3] W. D. Rudorf, A. Schierhon and M. Augustine, *Tetrahedron* **35**, 551, (1979).

[4] (a) R. G. Dubenko, V. D. Konysheva, E. F. Gorbenko and P. S. Pelkis, *Geterotsikl. Soedin.*, 1693, (1980); *Chem. Abstr.*, **94**, 139543p. (1981). (b) N. S. Ibrahim, K. U. Sadek, S. I. Aziz and M. H. Z. Elnagdi, *Naturforsch.*, **40b**, 129, (1985); *Chem. Abstr.*, **102**, 184935n, (1985).

[5] (a) M. Augustin, H. Dehne, W. D. Rudorf and P. Krey German(east) Patent 124302, (1977); *Chem. Abstr.*, **88**, 74292k, (1978). (b) W. D. Rudorf, *Z. Chem.*, **19**, 100, (1979). *Chem. Abstr.*, **91**, 5058p, (1979). (c) K. Gewald, U. Hain and M. Schmidt, (1986). *J. Prakt. Chem.*, **328**, 459, *Chem. Abstr.*, **106**, 156404c, (1987).

[6] (a) S. S. Bhattacharjee, C. V. Asokan, H. Ila and H. Junjappa, *Synthesis* 1062, (1982). (b) S. S. Bhattacharjee, H. Ila and H. Junjappa, *Synthesis* 410 (1983)

[7] (a) R. M. Mohareb and S. M. Sherif, *Arch. Pharm.*, **324(8)**, 469, (1991). (b) R. M. Mohareb, H. Z. Shams and S. I. Aziz, *J. Chem. Res. Synop.*, **5**, 154, (1992). (c) R. M. Mohareb, N. I. Abdel-Sayed and S. M. Sherif, *Phosphrous, Sulfur Silicon Relat. Elem.*, **63(1–2)**, 119, (1991). (d) R. M. Mohareb, S. M. Sherif, F. A. M. Abdel-Aal and I. A. Sayed Nadia, *Liebigs Ann. Chem.*, **11**, 1143 (1990).

[8] R. M. Mohareb and S. M. Sherif, *Arch. Pharm.*, **324(8)**, 469, (1991).
[9] (a) S. Rajappa, B. G. Advani and R. Sreenivasion, *Indian J. Chem.*, **12(1)**, 4, (1974); *Chem. Abstr* **81**, 37444w, (1974). (b) V. S. Petrenko, A. N. Borisevich, G. S. Stepura, G. P. Mozgovaya, L. S. Samoilenko and A. P. Rodionov, *Fiziol. Akt. Veshchestva* **21**, 39, (1989); *Chem. Abstr.*, **113**, 147174v, (1990).
[10] B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, (4thed; ELBS and Longman.) 736 (1978).
[11] R. N. Cowper and L. H. Duridson, *Organic Synthesis*, J. Wiley: New York, Collect. Vol. 2., 480 (1943).