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# Novel Synthesis of 5,6-Dihydro-4*H*-thieno[3,2-*b*]pyrrol-5-ones via the Rhodium(II)-Mediated Wolff Rearrangement of 3-(Thieno-2-yl)-3-oxo-2-diazopropanoates

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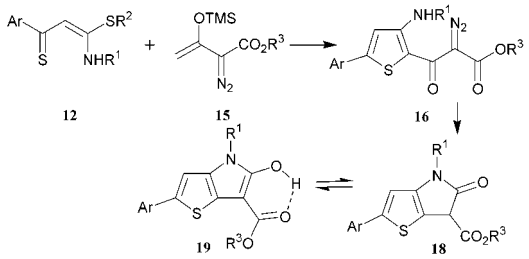
## ABSTRACT




**Treatment of thioaryolketene *S,N*-acetals 12 with $Hg(OAc)_2$ followed by addition of 2-diazo-3-trimethylsilyloxy-3-butenoic acid alkyl esters 15 in $CH_2Cl_2$ at room temperature gave 3-(3-alkylamino-5-arylthieno-2-yl)-3-oxo-2-diazopropanoates 16 in good yields. Subsequent reactions of 16 with a catalytic amount of $Rh_2(OAc)_4 \cdot 2H_2O$ in benzene at reflux afforded a mixture of 5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-5-ones 18 and the corresponding enols 19 in excellent yields.**

The exploration of synthetic methods for diverse thieno[3,2-*b*]pyrroles has received growing attention since it became known that some of them act as MCP-1 inhibitors useful as antiinflammatory agents, immunomodulators,[1] and bioisosteric analogues of the hallucinogen and seratonin agonist *N,N*-dimethyltryptamine.[2] Only a few methods are available for the synthesis of thieno[3,2-*b*]pyrroles. The first method, which has been most widely used, consists of condensation of an amino group with a suitably positioned carbonyl function of thiophenes, which are exemplified by either the cyclization of ethyl 2-formyl-3-thienylaminoacetate **1** into thieno[3,2-*b*]pyrroles **2** (X = $CO_2$Et, Y = H)[3] or reduction of ethyl (3-nitro-2-thienyl)pyruvate **3** with tin(IV) chloride followed by spontaneous cyclization of intermediate amino derivative[4] (Scheme 1). The second method involves the suitable insertion of nitrene intermediates. For instance, the action of triethyl phosphite on 3-nitro-3-styrylthiophenes **4** led to **2** (X = Ar, Y = H).[5] Alternatively, azidoacrylate **5** cyclized thermally to give **2** (X = $CO_2$Et, Y = H).[6]

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(1) Baker, A. J.; Kettle, J. G.; Faull, A. W. PCT Int. Appl. WO 9940, 914, GB Appl. 1998/ 3, 228; *Chem. Abstr.* **1999**, *131*, 170342d.
(2) Blair, J. B.; Marona-Lewicka, D.; Kanthasamy, A.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1999**, *42*, 1106.
(3) (a) Soth, S.; Farnier, M.; Paulmier, C. *Can. J. Chem.* **1978**, *56*, 1429. (b) Mamaev, V. P.; Lyubimova, E. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 1607.
(4) Gale, W. W.; Scott, A. N.; Snyder, H. R. *J. Org. Chem.* **1964**, *29*, 2160.
(5) (a) Srinivasan, K.; Srinivasan, K. G.; Balasubramanian, K. K.; Swaminathan, S. *Synthesis* **1973**, 313. (b) Chippendale, K. E.; Iddon, B.; Suschitzky, H. *J. Chem. Soc., Chem. Commun.* **1971**, 203.

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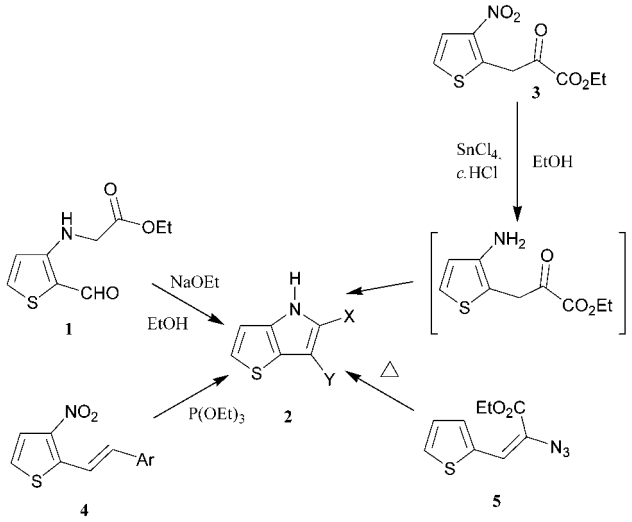
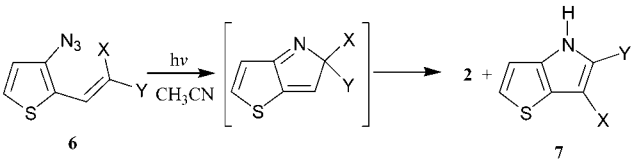
**Scheme 1**



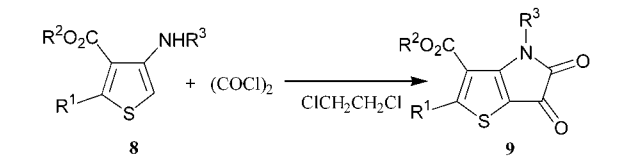
Photolysis of 3-azido-2-vinylthiophenes **6** (X = H, SMe, SOMe, Y = H, $SO_2Me$) gave **2** and thieno[3,2-*b*]pyrrole **7** via nitrene intermediates[7] (Scheme 2). Yields of **2** and **7** were variable depending on the substituents X and Y.

**Scheme 2**



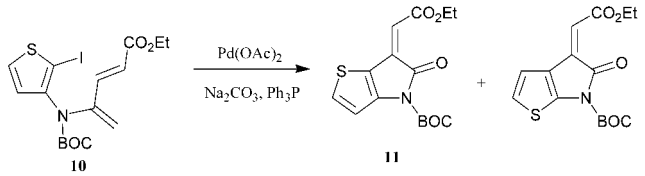
The third method involves the reactions of 4-alkoxycarbonyl-5-alkyl-3-arylaminothiophenes **8** with oxalyl chloride, yielding 5,6-dioxothieno[3,2-*b*]pyrroles **9**[8] (Scheme 3).

**Scheme 3**



In addition, Heck cyclization of *N*-BOC protected *N*-allylamino-*o*-iodothiophenes in DMF may be utilized for the synthesis of (*E*)-6-(carbethoxymethylene)-5-oxo-4-(*tert*-butoxycarbonyl)-5,6-dihydrothieno[3,2-*b*]pyrrole **11**[9] (Scheme 4).

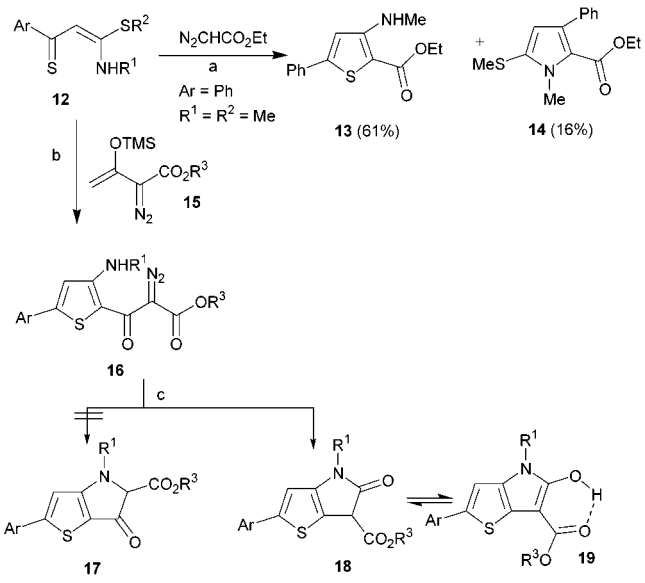
**Scheme 4**



All the methods reported have the drawback, as regards their general use for the synthesis of thieno[3,2-*b*]pyrroles bearing desired substituents, of difficult access to some of the starting materials.

In connection with an ongoing project on the development of the potential synthetic utility of thioaroylketene *S*,*N*-acetals **12**,[10] we became interested in the investigation of the reaction of **12** with carbenes since compound **12** possesses a variety of functional groups, i.e., C=S, C=C, RS, RNH, etc. Each of these functional groups is known to be susceptible to an electron-deficient carbene. However, it would be difficult to predict the reactivity of **12** toward carbenes. Preliminary experiments show that the reaction of **12** (Ar = Ph, $R^1$ = $R^2$ = Me) with ethyl α-diazoacetate in the presence of $Rh_2(OAc)_4 \cdot 2H_2O$ in $CH_2Cl_2$ at room temperature gave thiophene derivative **13** (61%) and pyrrole derivative **14** (16%) (Scheme 5). Using this methodology, we intended to prepare 5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-6-ones **17** by the reaction of 3-(3-alkylamino-5-arylthieno-2-yl)-3-oxo-2-diazopro-

**Scheme 5**[a]



[a] Reagents: (a) $Rh_2(OAc)_4 \cdot 2H_2O$, $CH_2Cl_2$, rt; (b) $Hg(OAc)_2$, $CH_2Cl_2$, rt; (c) $Rh_2(OAc)_4 \cdot 2H_2O$, PhH, reflux.

(6) (a) Soth, S.; Farnier, M.; Paulmier, C. *Can. J. Chem.* **1978**, *56*, 1710. (b) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194.

(7) Gairns, R. S.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1985**, 1818.

(8) (a) Shvedov, V. I.; Vasiléva, V. K.; Kharizomenova, I. A.; Grinev, A. N. *Khim. Geterotsikl. Soedin*, **1975**, 767. (b) Shevedov, V. I.; Vasiléva, V. K.; Kharizomenova, I. A.; Otkrytiya, A. N. Grinev. *Izobret., Prom. Obraztsy, Tovarnye Znaki* **1973**, *50*, 62.

panoates **16**, which may be prepared from **12** and 2-diazo-3-trimethylsilyloxy-3-butenoate **15**, using a rhodium(II) catalyst under the same conditions. It was envisaged that **17** would be formed upon insertion of carbene or carbenoid, generated from **16**, into the N−H bond of the alkylamino group at C-3. This would occur in view of the formation of various products by tandem cyclization−cycloaddition sequence of rhodium(II) carbenoids and application of the resulting metallocarbenoids to a wide variety of heterocycles.[11]

Compounds **12**[10] and **15**[11] were prepared according to documented procedures. Treatment of **12** with $Hg(OAc)_2$ (1.2 equiv) in $CH_2Cl_2$ at room temperature, followed by addition of **15** (1 equiv) gave diazocarbonyl compounds **16** in good yields as expected. All of the compounds **16** were stable in air and recrystallizable from a mixture of $CH_2Cl_2$ and *n*-hexane. Subsequent treatment of **16** with a catalytic amount of $Rh_2(OAc)_4 \cdot 2H_2O$ (0.5 mg) in benzene for 30 min at reflux afforded 5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-5-ones **18** rather than thieno[3,2-*b*]pyrrol-6-ones **17**. The $^1H$ NMR spectra (300 MHz, $CDCl_3$) of **18** showed a singlet at 4.42−4.60 ppm, assigned to a methine proton of **18**, and two sets of alkyl protons corresponding to *N*-alkyl and alkoxycarbonyl groups, which indicates that the products exist as a mixture of keto forms **18** and enol forms **19**. The ratios of **18** and **19** were determined on the basis of the intensities of *N*-alkyl proton absorptions.[12] Yields of compounds **16**, **18**, and **19** are summarized in Table 1.

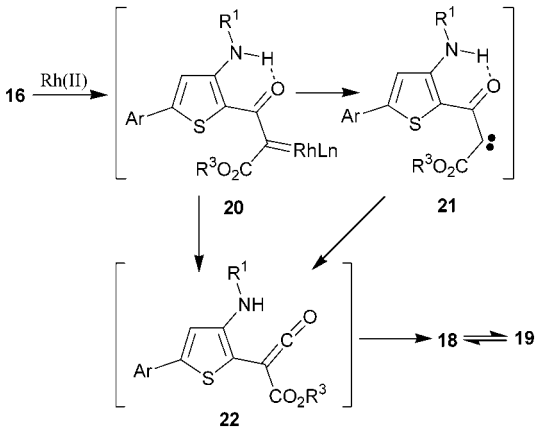
**Table 1.** Yields of Compounds **16**, **18** + **19**, and **23**

| | | | | | yield,[a] % | | |
|---|---|---|---|---|---|---|---|
| entry | Ar | $R^1$ | $R^3$ | compd | **16** | **18**+**19** (keto: enol) | **23** |
| 1 | Ph | Me | Et | **a** | 91 | 99 (1:1.26) | 89 |
| 2 | Ph | Me | *t*-Bu | **b** | 87 | 94 (1:0.87) | 89 |
| 3 | Ph | Et | Et | **c** | 71 | 90 (1:1.46) | 86 |
| 4 | Ph | Et | *t*-Bu | **d** | 79 | 91 (1:0.78) | 91 |
| 5 | Ph | Bn | Et | **e** | 73 | 91 (1:1.23) | 96 |
| 6 | Ph | Bn | *t*-Bu | **f** | 82 | 89 (1:0.70) | 91 |
| 7 | 4-$MeOC_6H_4$ | Me | Et | **g** | 71 | 97 (1:0.88) | 87 |
| 8 | 4-$MeOC_6H_4$ | Me | *t*-Bu | **h** | 68 | 95 (1:0.65) | 90 |
| 9 | 4-$MeOC_6H_4$ | Et | Et | **i** | 74 | 95 (1:1.11) | 75 |
| 10 | 4-$MeOC_6H_4$ | Et | *t*-Bu | **j** | 71 | 93 (1:0.77) | 87 |
| 11 | 3-$ClC_6H_4$ | Me | Et | **k** | 71 | 92 (1:2.07) | 86 |
| 12 | 3-$ClC_6H_4$ | Et | Et | **l** | 72 | 90 (1:2.33) | 88 |

[a] Isolated yields. Compounds **16** are yellow solids except for **16h** (yellow liquid). Mixtures of compounds **18** and **19** are pale yellowish sticky liquids. Compounds **23** are pale yellow solids.

The exclusive formation of thieno[3,2-*b*]pyrrol-5-ones may be rationalized by assuming a *cis* relationship of rhodium carbenoid and the keto carbonyl group (Scheme 6). It is

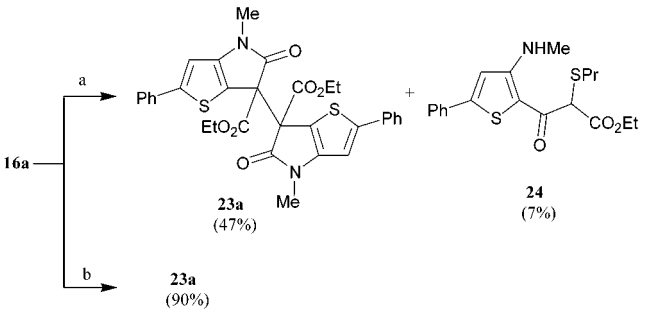
**Scheme 6**




envisaged that there exists a hydrogen bond between the carbonyl oxygen and a hydrogen on an alkylamino group as depicted in the intermediates **20** and **21**. A *cis* relationship of diazo and carbonyl is highly preferred in diazo ketones of the type $RCOCHN_2$.[13] The *cis* form represents a desirable feature of the migrating group being *trans* to the leaving group. As a result, the rhodium carbenoids **20** and **21** undergo Wolff rearrangement to give a ketene **22**. The ketene functional group would be rapidly trapped by an intramolecular nucleophilic attack of the alkylamino group at C-3 of the thienyl ring to give **18**.

Treatment of a mixture of **16a** (70 mg, 0.213 mmol) and *n*-PrSH (486 mg, 6.39 mmol) with $Rh_2(OAc)_4 \cdot 2H_2O$ (0.5 mg) in benzene for 3 h at reflux gave **23a** (47%), a dimer of **18a** together with an insertion product **24** (6 mg, 7%) and unknown mixtures, which are inseparable by chromatography (Scheme 7). On the other hand, the reaction of **16a** (70 mg,

**Scheme 7**[a]




[a] Reagents: (a) *n*-PrSH, $Rh_2(OAc)_4 \cdot 2H_2O$ , PhH, 3 h; (b) , $Rh_2(OAc)_4 \cdot 2H_2O$, PhH, reflux, 30 min

0.213 mmol) with ethyl vinyl ether (460 mg, 6.39 mmol) in the presence of the same catalyst for 30 min at reflux gave **23a** in 90% yield.

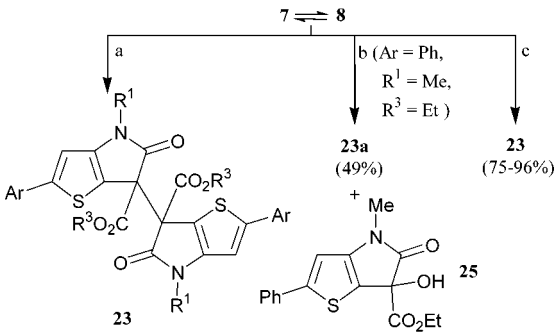
It has been found that compounds **18** were labile and underwent slow dimerization reactions to give compounds

(9) Wensbo, D.; Annby, U.; Gronowitz, S. *Tetrahedron* **1995**, *51*, 10323.
(10) Kim, B.; Kim, K. *J. Org. Chem.* **2000**, *65*, 3690.
(11) (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (c) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (d) Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936.

**23**, whose structures were confirmed by an X-ray crystal structure study of **23a**.

To confirm the significance of oxygen dissolved in the solution, oxygen gas was bubbled into a solution of a mixture of **18a** and **19a** (49 mg, 0.163 mmol) in $CH_2Cl_2$ (30 mL) for 5 days at room temperature. From the reaction were isolated a hydroxyl compound **25** (7 mg, 14%), **23a** (24 mg, 49%), and unknown mixtures, which were inseparable by chromatography (Scheme 8).

**Scheme 8**[a]



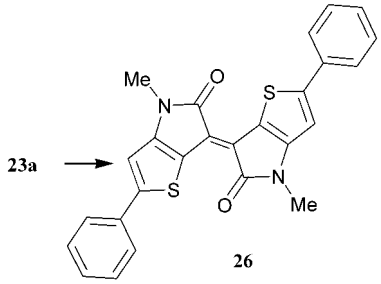

[a] Reagents: (a) $CH_2Cl_2$, rt; (b) $O_2$, $CH_2Cl_2$, rt, 5 days; (c) $Cu(OAc)_2 \cdot H_2O$, EtOH, $N_2$, rt hydroxyl compound **25** (7 mg, 14%), **23a** (24 mg, 49%), and unknown mixtures, which were inseparable by chromatography (Scheme 8).

Interestingly, treatment of a mixture of **18** and **19** with $Cu(OAc)_2 \cdot H_2O$ (1.2 equiv), which has been well-known to give a single good electron oxidant,[14] for 30 min in EtOH (30 mL) at room temperature under nitrogen atmosphere gave **23** in excellent yields. Yields of **23** are summarized in Table 1.

(12) For $R^1$ = Me (entries 1, 2, 7, 8, and 11), the absorptions of the Me protons of **18** and **19** are 3.25−3.26 and 3.58−3.60 ppm, respectively. For $R^1$ = Et (entries 3, 4, 9, 10, and 12), the absorptions of the $CH_2$ protons of **18** and **19** are 3.74−3.77 and 4.02−4.05 ppm, respectively. For $R^1$ = Bn (entries 5 and 6), the absorptions of the benzylic protons of **18** and **19** are 4.82−4.95 and 5.15 ppm, respectively.

It is worth noting that hydrolysis of **23a** with aqueous NaOH (1%) in EtOH at reflux gave an oxidative decarboxylation product **26** in 53% yield (Scheme 9).

**Scheme 9**[a]




[a] Reagents: aqueous NaOH (1%), EtOH, reflux.

The structures of **26** were determined on the basis of spectroscopic ($^1H$ and $^{13}C$ NMR, IR, MS) and analytical data.

In conclusion, we have found that treatment of 3-(3-alkylamino-5-arylthieno-2-yl)-3-oxo-2-diazopropanones, readily prepared starting from thioaroylketene *S*,*N*-acetals, $Hg(OAc)_2$, and trimethylsilyl enol ether of alkyl α-diazoacetate, with a catalytic amount of $Rh_2(OAc)_4 \cdot 2H_2O$, underwent Wolff rearrangement yielding 5,6-dihydro-4*H*-thieno[3,2-b]-pyrrol-5-ones in excellent yields.

**Acknowledgment.** This work was supported by the Brain Korea 21 program.

**Supporting Information Available:** Copies of $^1H$ NMR, IR, and elemental analyses of **13**, **14**, **16**, a mixture of **18** and **19**, **23**, **24**, **25**, and **26**; $^{13}C$ NMR spectra of **13**, **16**, and **26**; X-ray crystallographic data for **23a**; and an ORTEP drawing of **23a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Harrison, J. F. In *Carbene Chemistry*, 2nd ed.; Kirmse, W.; Academic Press: New York, 1971; Chapter 12, pp 457−503.

(14) Nonhebel, D. C.; Walton, J. C. *Free-Radical Chemistry*, Cambridge University Press: New York, 1974; Chapter 10, pp 305−416.