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Novel synthesis of 3-alkyl-2,5-diaryl-1,4-oxathiepin-7-ones

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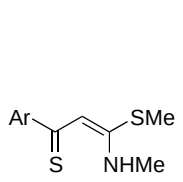
Abstract—*N*-Acetyl-*N*-methyl-3-aryl-3-[1-(aroyl)ethylthio]-2-propaneamides, prepared from thioaroylketene *S*,*N*-acetals, $Hg(OAc)_2$ and silyl enol ethers of aryl-1-propanones in CH_2Cl_2 at rt, reacted with NaH in THF to give the title compounds in excellent yields.

Although some of dihydro-1,4-oxathiepins appeared to be useful in the preparation of drugs and agrochemicals[1] and antifungal compounds,[2] little has been explored about their synthetic methods and reactions. A survey of the literature shows that 5*H*-1,4-oxathiepin-2(3*H*)-one was obtained by intramolecular ene reaction of the intermediate allyl thioxoacetate, generated by thermolysis of pent-4-enyl 2-thiabicyclo-[2,2,1]hept-5-ene-endo-3-carboxylate.[3] 2,3-Dihydro-5-(6-hydroxyheptyl)-1,4-oxathiepin-7-one was observed as a by-product in the total synthesis of (±)-diplodialide-A.[4] Reaction of polyfluoro-2-alkynoic acids with thioethanol gave polyfluorinated oxathiepins.[5] Similarly, the reaction of ethyl 2-thiobenzoates with chlorohydrin and glycerol chlorohydrin gave the corresponding intermediates which were converted to benzoxathiepinones.[6] All the reactions lack the generality for the synthesis of 1,4-oxathiepinones. In addition, it is interesting to note that much has been studied for other seven-membered analogs, i.e. 1,4-dioxepinones and 1,4-dithiepinones compared with that for 1,4-oxathiepinones.[7]

We have previously reported that thioaroylketene *S*,*N*-acetals **1** reacted readily with enolizable ketones in the presence of mercury(II) acetate in CH_2Cl_2 at rt to give 2-substituted 5-aryl-3-methylaminothiophenes via nucleophilic attack of the enolic carbon to the imino carbon atom of the intermediate **2** (path a).[8] In a continuation of our research on the synthetic utility of compound **1**, we were interested in finding ketones whose enolic carbon would attack the sulfur atom (path b) instead of the imino carbon atom, so that the carbanion **3** generated at α position to the carbonyl group in the presence of base would be utilized as an intermediate for the synthesis of a new compound. With this in mind, the reaction of **1** with trimethylsilyl enol ethers of alkyl aryl ketones were studied. We wish to report the preliminary result.

The reaction of **1a** (Ar = Ph) with acetophenone for 1 h under the same conditions as described previously[9] afforded 2-methyl-5-phenylisothiazol-3-one (**4**) (65%) along with thiophene derivative **5a** (Ar = R^1 = Ph) (9%), whereas the reaction with trimethylsilyl enol ether of acetophenone gave **5a** in 75% yield[10] (Scheme 1). Similarly, the reactions with silyl enols ether of methyl ketones under the same conditions gave thiophene derivatives **5b–d** (**5b**, Ar = Ph, R^1 = 4-ClC_6H_4, 79%; **5c**, Ar = Ph, R^1 = CH=CHOMe, 69%; **5d**, Ar = Ph, R^1 = CH=C(OMe)TMS, 66%).



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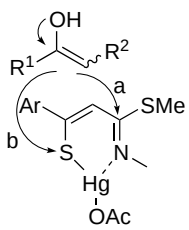

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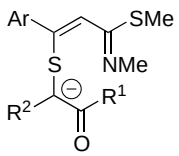

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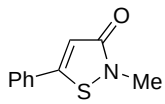

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Keywords: ketene acetals; mercury and compound; thiophenes; enol ethers.

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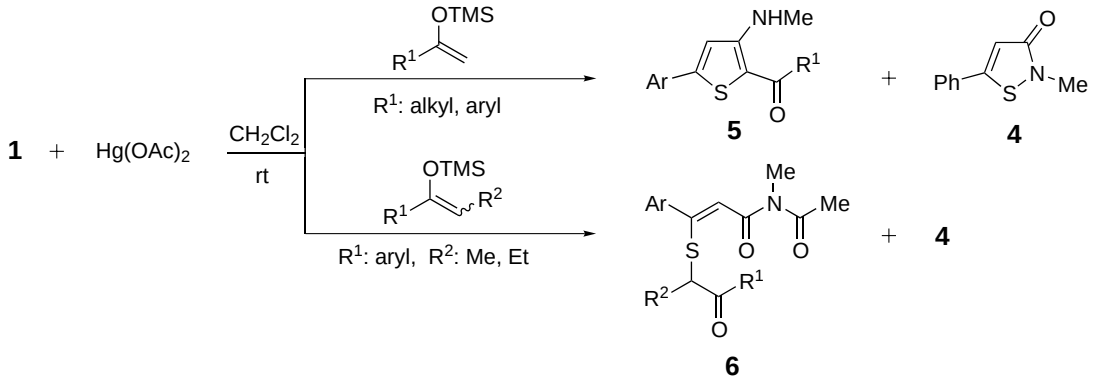


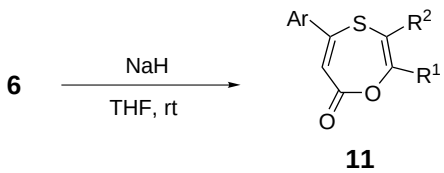
Scheme 1.

In contrast, with silyl enol ethers of 1-aryl-1-propanones and 1-aryl-1-*n*-butanones the corresponding *N*-acetyl-*N*-methyl 3-aryl-3-[1-(aroyl)alkylthio]-2-propen-amides **6** were obtained as major products together with a small amount of **4**. No thiophene derivatives **5** were detected. The reaction with silyl enol ether of 1-(4-bromophenyl)-2-methylpropanone, however, gave compounds **10** and **4** in 7 and 41% yields, respectively. This result indicates that steric effect at the enolic carbon atom is crucial to the formation of compound **6**. (Scheme 2). Reaction times and yields of compounds **4** and **6** are summarized in Table 1.

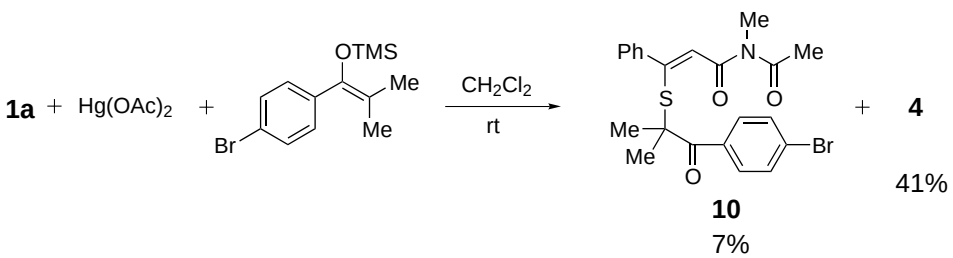
The structures of compounds **6a**–**g** were determined based on the spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) and elemental analysis.

It has been found that treatment of compounds **6** with NaH in THF at rt gave 3-alkyl-2,5-diaryl-1,4-oxathiepin-7-ones **11** in good to excellent yields[11] (Scheme 3). Reaction times and yields of compounds **11** are summarized in Table 2.

Although 2,3-dihydro-1,4-oxathiepin-7-one was reported, to the best of our knowledge, compounds **11** are the first examples for 1,4-oxathiepin-7-ones.



Scheme 3.



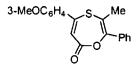
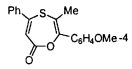
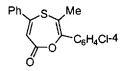
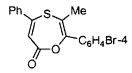
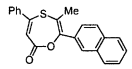
Scheme 2.

Table 1. Reaction times and yields of compounds **4** and **6**

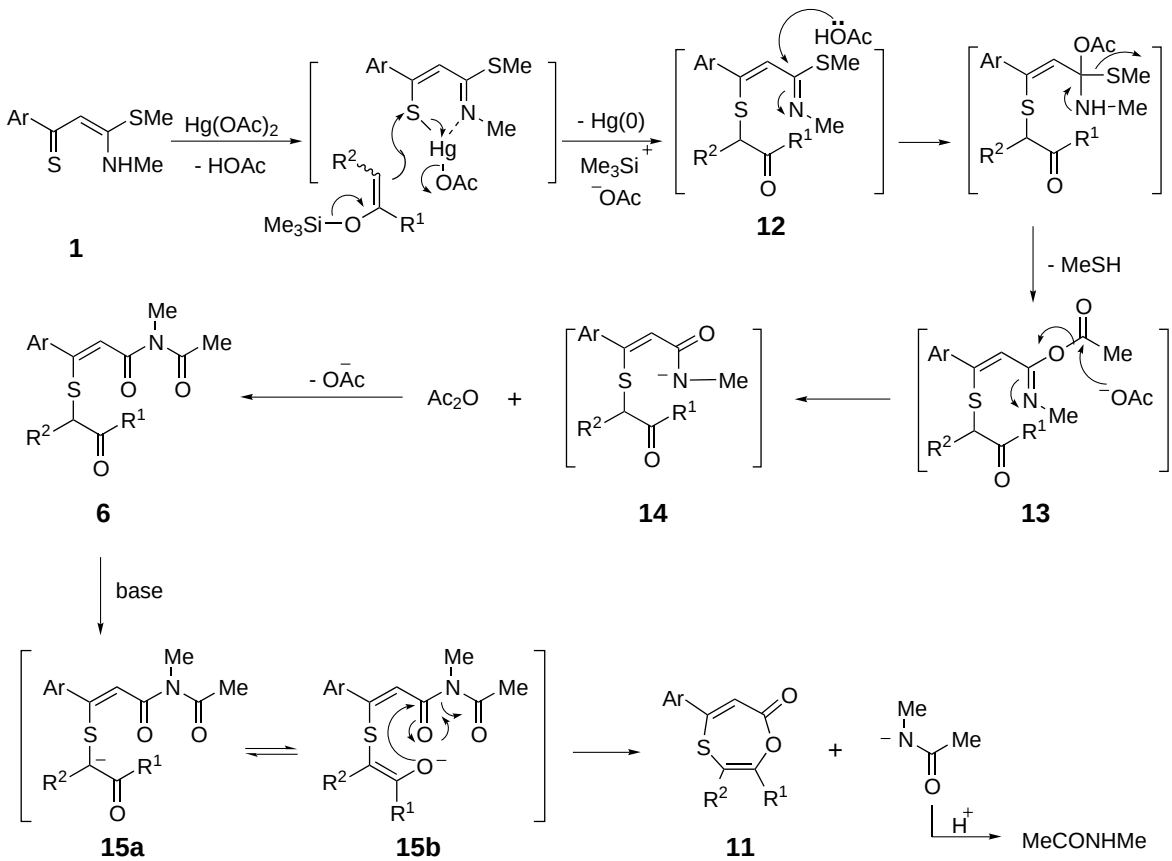
Compound	Ar	R^1	R^2	Time (h)	Yield[a] (%)
6a	Ph	Ph	Me	3	58 (5)
6b	Ph	Ph	Et	3	50 (trace)
6c	3-$MeOC_6H_4$	Ph	Me	3	58 (trace)
6d	Ph	4-$MeOC_6H_4$	Me	2	47 (5)
6e	Ph	4-ClC_6H_4	Me	2	44 (5)
6f	Ph	4-BrC_6H_4	Me	2	47 (3)
6g	Ph	2-Naphthyl	Me	3	53 (5)

[a] Isolated yields. Number in parentheses represent yields of compound **4**.

Table 2. Reaction times, yields and mp of compounds **11**

Compound		Time (h)	Yield[a] (%)	Mp (°C)
11a		0.5	93	90 – 91[b]
11b		0.5	85	Liquid
11c		1	87	61 – 62[b]
11d		1	85	96 – 98[c]
11e		1	85	92 – 94[c]
11f		0.5	85	119 – 120[c]
11g		1	73	125 – 126[c]

[a] Isolated yields. [b] Recrystallized from a mixture of ethyl ether and *n*-hexane. [c] Recrystallized from a mixture of EtOAc and *n*-hexane.



Scheme 4.

The mechanism for the formation of **6** may be rationalized based on the formation of an intermediate **12**, which then undergoes acetolysis to give imidoyl acetate **13** (Scheme 4). This species are known to be unstable.[12] Acetolysis of **13** would lead to acetic anhydride and an intermediate **14**, which lead to amide **6**. The formation of compounds **11** may be explained by an intramolecular nucleophilic attack of the enolate ion **15b**, existing as an equilibrium mixture with its carbanion ion **15a**, on the amide carbonyl carbon.

Acknowledgements

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10. General procedure: To a mixture of thioaroylketene *S*,*N*-acetals (0.179–0.224 mmol) and $Hg(OAc)_2$ (0.270–0.336 mmol) in CH_2Cl_2 (8 ml) at rt was added silyl enol ethers (0.177–0.225 mmol). The mixture was stirred for an appropriate time (refer to Table 1). After solids were filtered, the solvent of the filtrated was evaporated in vacuo to give a residue which was chromatographed on a silica gel (1.5×15 cm). (i) Elution with a mixture of EtOAc and *n*-hexane (1:4) gave compounds **5**. (ii) For compounds **6** elution with the same solvent mixture (1:3) gave **6**. Elution with the same solvent mixture (1:1) gave compound **4**.
Selected compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (3H, d, $J=7.1$ Hz, $CHCH_3$), 2.45 (3H, s, $COCH_3$), 3.22 (3H, s, NCH_3), 4.44 (1H, q, $J=7.1$ Hz, $CHCH_3$), 6.52 (1H, s, vinyl), 7.26–7.35 (7H, m, ArH), 7.49–7.53 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.09, 26.24, 32.04, 45.35, 121.021, 128.20, 128.26, 128.40, 128.74, 129.25, 133.11, 135.19, 138.70, 157.03, 167.62, 173.15, 197.68; IR (neat) 1667, 1094, 970, 696 cm^{-1}; FAB MS *m*/*z* 368 (M^++1, 21.0) 326 (5.3), 295 (100), 234 (74.9), 202 (17.1). Anal. calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81; S, 8.73. Found: C, 68.76; H, 5.81; N, 3.88; S, 8.70.
11. Typical procedure: To a solution of NaH (60%, 3 mg, 0.075 mmol) in THF (5 mL) under a nitrogen atmosphere **6a** was added dropwise (16 mg, 0.044 mmol) in 2 mL portions. The mixture was stirred for 30 min, followed by addition of aqueous $NaHCO_3$, which was extracted with ethyl ether (20 mL×2). The extracts were dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel (1.5×15 cm) with a mixture of EtOAc and *n*-hexane (1:6) as an eluent to give **6a** (12 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (3H, s, Me), 7.17 (1H, s, vinyl), 7.25–7.28 (1H, m, ArH), 7.33–7.39 (2H, m, ArH), 7.35–7.57 (4H, m, ArH), 7.62–7.68 (1H, m, ArH), 8.20–8.24 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.46, 117.80, 124.36, 125.19, 127.50, 128.65, 128.85, 129.22, 130.20, 133.69, 134.12, 138.66, 143.50, 164.39; IR (neat) 1736, 1592, 1562, 1499, 1443, 1262, 1112, 1051, 754, 707 cm^{-1}; MS *m*/*z* 294 (M^+, 27.0), 189 (2.7), 105 (100). Anal. calcd for $C_{18}H_{14}O_2S$: C, 64.84; H, 6.35; S, 814.42. Found: C, 64.76; H, 6.28; S, 14.29.
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