JOC Article

A New Facile Approach to the Synthesis of 3-Methylthio-Substituted Furans, Pyrroles, Thiophenes, and Related Derivatives

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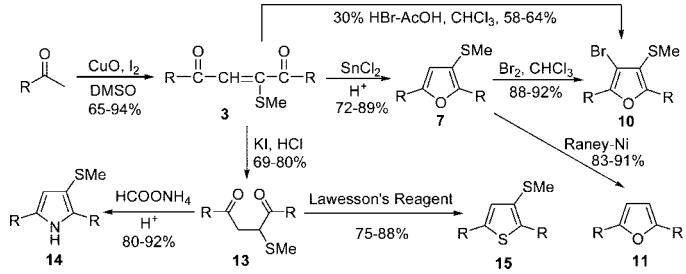

2-(Methylthio)-1,4-diaryl-2-butene-1,4-dione (**3**) are prepared from readily available aryl methyl ketones in the presence of copper(II) oxide, iodine, and dimethyl sulfoxide. The success of the cross-coupling reaction of 4-chloroacetophenone with 2-acetylthiophene confirms a proposed self-sorting tandem reaction mechanism. Both *Z*- and *E*-isomers of compound **3** are readily converted into the corresponding 3-methylthio 2,5-diaryl furan **7** in good yield through a domino process involving the reduction of the double bond followed by the Paal−Knorr furan synthesis. Meanwhile, 4-bromo-3-methylthio 2,5-diaryl furan **10** is obtained either by the treatment of furan **7** with molecular bromine or by the treatment of diketone **3** with 30% hydrogen bromide in acetic acid solution in one pot. Removal of the methylthio group is accomplished by the treatment of **7** with Raney Ni in ethanol, which affords the diaryl-substituted furan **11** in excellent isolated yield. Selective reduction of the double bond of compound **3** leads to the formation of the saturated 1,4-diketone **13**, which is easily converted to the corresponding 3-methylthio-2,5-diaryl-substituted pyrrole **14** and thiophene **15** via the Paal−Knorr cyclization reaction.

Introduction

Substituted furans, thiophenes, and pyrroles represent three important classes of five-membered heterocycles that are found as structural elements in many natural products, as well as pharmaceutically important substrates.[1–3] They also can be employed as useful intermediates in synthetic organic chemistry,[4] material science,[5] nonlinear optics,[6] and supramolecular chemistry as molecular sensors and other devices.[7] Therefore, a large number of synthetic methods have been developed in recent years to generate these substituted five-membered heterocycles.[8–11] Among the reported methods, the classical

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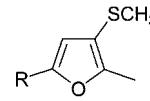
Paal−Knorr[12] reaction (cyclocondensation of 1,4-dicarbonyl compounds) is still the most frequently used for the synthesis of these five-membered heterocycles.

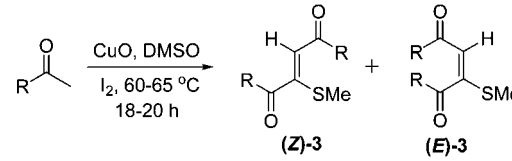
Sulfur-containing aromatics are attractive candidates for organic semiconductors[13] and can act as unique coordination compounds for electronic, magnetic, and optical materials.[14] Many 3-thio-substituted furan derivatives (such as thioethers **1** and **2**, Scheme 1) have been identified in coffee and cooked beef.[15] In addition, alkylthio-substituted heterocycles are particularly attractive intermediates that have found widespread usage in organic synthesis. They can undergo a variety of reactions[16,17] including addition/elimination, nickel-catalyzed Grignard coupling, Michael additions, ortho-metalation, acid hydrolysis to butenolides, [4 + 2]-cycloaddition reactions, and the Liebeskind−Srogl reaction.[18] Although many synthetic procedures are available for their formation,[19] most of the existing methods often require harsh conditions and are frequently based on the use of a preexisting heterocycle.

SCHEME 1



1 R = H
2 R = Me

SCHEME 2



The formation of carbon−carbon bonds is central to organic synthesis because it provides the carbon skeleton that defines the structure and function of an organic compound. Although many excellent methods have been published, the direct carbon−carbon bond-forming reaction between two sp^3 C−H bonds is still a challenge.[20] Recently, we reported a carbon−carbon double-bond-forming reaction for the preparation of 2-methylthio-substituted 1,4-diketones from readily available (hetero)aryl methyl ketones (Scheme 2),[21] which is a novel carbon−carbon double-bond-forming reaction between the sp^3 C−H bonds of two methyl groups. This is also a simple, effective, and interesting approach to the 1,4-diketones compared with the previously reported methods[22] and an attractive way to introduce the methylthio group into these molecules from inexpensive dimethyl sulfoxide. In this paper, the scope of the substrates is extended to other heteroaryl methyl ketones and the reaction mechanism is further confirmed via cross-coupling reactions. In addition, the Paal−Knorr cyclization reactions of these 1,4-diketones to give methylthio-substituted furans, pyrroles, and thiophenes and their derivatives have been investigated. These have been found to proceed in good yield.

Results and Discussion

Homocoupling of aryl methyl ketones in the presence of iodine, copper(II) oxide, and dimethyl sulfoxide affords 2-me-

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TABLE 1. Formation of 2-Methylthio 1,4-Diketones via Homocoupling of (Hetero)aryl Methyl Ketones

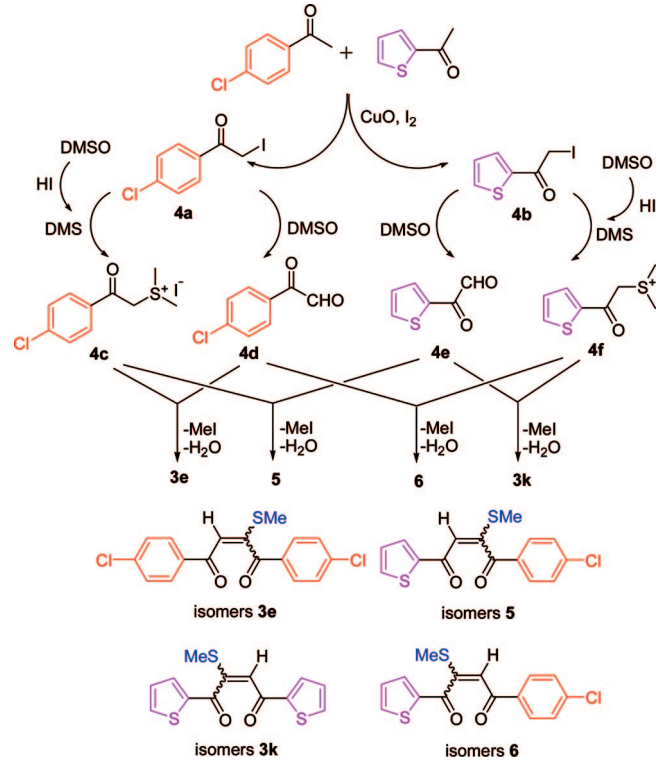
entry	R	3	yield[a] (%, *Z*/*E*)	entry	R	3	yield[a] (%, *Z*/*E*)
1	C_6H_5	**3a**	86 (86/14)	9	2-naph	**3i**	89 (63/37)
2	4-MeC_6H_4	**3b**	94 (81/19)	10[b]	2-furyl	**3j**	81
3	4-$MeOC_6H_4$	**3c**	81 (86/14)	11	2-thienyl	**3k**	80 (93/7)
4	4-$EtOC_6H_4$	**3d**	86 (93/7)	12	5-Br-2-thienyl	**3l**	74 (81/19)
5	4-ClC_6H_4	**3e**	85 (70/30)	13	5-Cl-2-thienyl	**3m**	70 (84/16)
6	4-BrC_6H_4	**3f**	92 (70/30)	14	3-thienyl	**3n**	77 (88/12)
7	4-$NO_2C_6H_4$	**3g**	71 (57/43)	15[b]	2-benzofuryl	**3o**	65
8	1-naph	**3h**	88 (63/37)				

[a] Isolated yield. [b] *E*-isomers are not isolated.

thylthio-substituted 1,4-diketones in good yield (Table 1, entries 1–9).[21] Unsubstituted heteroaryl methyl ketone substrates also give good results (Table 1, entries 10 and 11). Since the building blocks for the synthesis of oligomers that are used in the material sciences are often the mixed thiophene/furan/pyrrole units,[23] we first extended the scope of the reaction to the substituted (or different position-substituted) heteroaryl methyl ketone substrates. For example, heating a mixture of 5-bromo-2-acetylthiophene, iodine, copper(II) oxide, and dimethyl sulfoxide at 60–65 °C for about 18 h produces the expected diketones ***3l*** in 74% overall yield (*Z*/*E* = 81/19) (Table 1, entry 12). Similarly, substrates 5-chloro-2-acetylthiophene, 3-acetylthiophene, and 2-acetylbenzofuran also give the desired products **3m**, **3n**, and **3o** in 70%, 77%, and 65% overall yields, respectively (Table 1, entries 13–15). *Z*-isomers are the major products due to their better thermodynamic stability than *E*-isomers during the dehydrating process of the intermediate.[21] The *Z*/*E*-stereoconfiguration determination for compounds **3** was accomplished by means of one- and two-dimensional NMR experiments[24] including ^1H, ^{13}C, gCOSY, gHSQC, gHMBC, and NOESY. The ^1H NMR spectra show that the protons of the SCH_3 appear as a singlet at 2.45–2.52 and 2.16–2.29 ppm in *E*-isomers and *Z*-isomers, respectively, while the vinyl hydrogen (H-2) of *E*-isomers and *Z*-isomers presents a singlet in the range 6.69–6.96 and 6.89–7.03 ppm, respectively. In other words, the methyl protons of *Z*-configuration in this system resonate at higher field than those of *E*-configuration, but the vinyl hydrogen of *Z*-configurational compounds exhibits resonance at lower field than that of *E*-configurational compounds.

Inspired by the successful synthesis of 1,4-diketones by the homocoupling reaction, and to confirm further the proposed self-sorting tandem reaction mechanism,[21] we investigated the cross-coupling reaction between two representative substrates 4-chloroacetophenone and 2-acetylthiophene under the above-noted standard conditions. As shown in Scheme 3, according to the reaction mechanism, heating a mixture of equimolar 4-chloroacetophenone and 2-acetylthiophene should give eight 1,4-diketones. This complex reaction process may proceed as follows: First, α-iodoketones **4a** and **4b**, obtained by iodination of the methyl ketones with copper(II) oxide and iodine, likely are sequentially oxidized by dimethyl sulfoxide to **4d** and **4e**. Thereafter, **4a** and **4b** react with dimethyl sulfide (DMS), which is readily produced from dimethyl sulfoxide in high yield by the presence of HI, which is formed in the first step. This leads to the sulfur ylides **4c** and **4f**, respectively. Then **4d** condenses

SCHEME 3. The Cross-Coupling Reaction



with **4c** or **4f** (**4e** with **4c** or **4f**) in aldol-type reactions to produce intermediates which after the loss of MeI are then dehydrated to yield 1,4-diketones **3e** or **6** (**5** or **3k**). Fortunately, the eight products could be identified by HPLC-MS analysis of the crude isolated reaction mixture, as shown in Figure 1 [the peaks of (*Z*)-**5** and (*Z*)-**6** overlapped, see the Supporting Information for details). Furthermore, the heterocoupling products (*Z*)-**5** and (*Z*)-**6** were also isolated by column chromatography in 24% and 6% yields, respectively. Furthermore, the structure of (*Z*)-**5** is confirmed by an X-ray crystal analyses (see the Supporting Information).

Next, we attempted to synthesize 3-methylthio 2,5-diaryl furans in one pot from the already synthesized unsaturated 1,4-diketones through a domino process involving the reduction of the double bond followed by a Paal−Knorr furan cyclization. As shown in Scheme 4, reduction of (*Z*)-**3a** with stannous chloride in the presence of concentrated hydrochloric acid in acetic acid at reflux[25] resulted in the formation of furan **7a** in 85% isolated yield within 30 min (Table 2, entry 1). **7a** was also obtained in 87% yield starting from (*E*)-**3a** under the same reaction conditions (Table 2, entry 2). When diketones (*Z*)-**3** bearing electron-donating Me, OMe, and OEt groups or moderately electron-withdrawing Cl or Br atoms at the C-4 position of the phenyl ring were heated in this way, furans **7b–f** were obtained in 83–89% yields (Table 2, entries 3 and 5–8). The structure of **7b** is unambiguously supported by an X-ray crystal structure analysis (see the Supporting Information). However, in the case of substrate **3g** bearing an electron-withdrawing NO_2 group on the phenyl ring, the reaction gave a complicated mixture and the expected furan **7g** was not observed, which accorded with the published results (Table 2,

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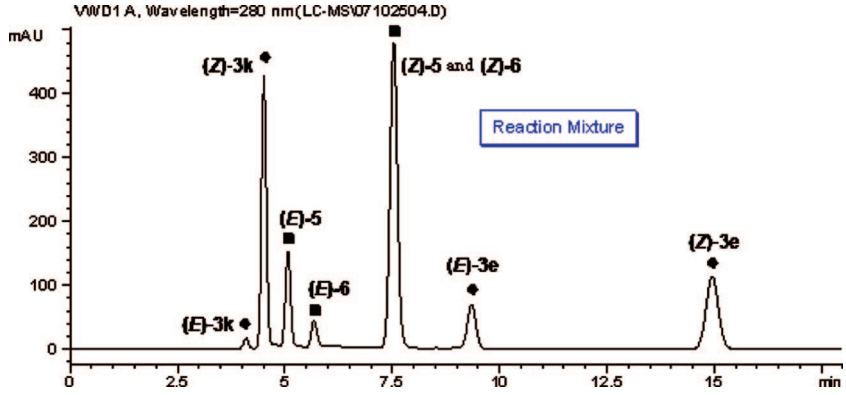


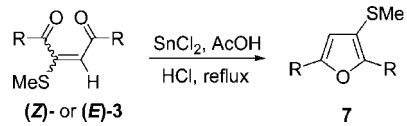
FIGURE 1. HPLC-MS analysis of the crude isolated reaction mixture. Chromatography was performed on a Hypersil ODS2 column (4.6250 mm, 5 μm) with methanol–water (75%:25%) as the mobile phase. The detection wavelength was 280 nm (see the Supporting Information for details). Homocoupling and heterocoupling products are marked with a circle (●) or a square (■), respectively.

TABLE 2. Synthesis of 3-Methylthio-2,5-diaryl Furans

entry	reactants	R	products	yield[a] (%)	entry	reactants	R	products	yield[a] (%)
1	(*Z*)-**3a**	C_6H_5	**7a**	85	10	(*Z*)-**3g**	4-$NO_2C_6H_4$	**7g**	0
2	(*E*)-**3a**	C_6H_5	**7a**	87	11	(*Z*)-**3h**	1-naph	**7h**	80
3	(*Z*)-**3b**	4-MeC_6H_4	**7b**	89	12	(*E*)-**3h**	1-naph	**7h**	82
4	(*E*)-**3b**	4-MeC_6H_4	**7b**	90	13	(*Z*)-**3i**	2-naph	**7i**	84
5	(*Z*)-**3c**	4-$MeOC_6H_4$	**7c**	88	14	(*Z*)-**3j**	2-furyl	**7j**	trace
6	(*Z*)-**3d**	4-$EtOC_6H_4$	**7d**	85	15	(*Z*)-**3k**	2-thienyl	**7k**	78
7	(*Z*)-**3e**	4-ClC_6H_4	**7e**	83	16	(*Z*)-**3n**	3-Thienyl	**7n**	75
8	(*Z*)-**3f**	4-BrC_6H_4	**7f**	85	17	(*Z*)-**3o**	2-benzofuryl	**7o**	69
9	(*E*)-**3f**	4-BrC_6H_4	**7f**	88					

[a] Isolated yield.

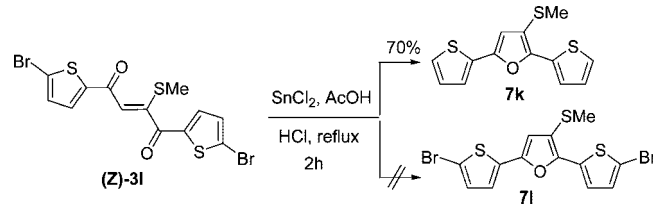
SCHEME 4



entry 10).[26] To our satisfaction, when the R groups of the *Z*-isomers are naphthyl, thienyl, or benzofuryl, the corresponding furans (**7h**, **7i**, **7k**, **7n**, and **7o**) were obtained in 69–84% yields (Table 2, entries 11, 13, and 15–17). Unfortunately, we failed to obtain furan **7j** due to the difficulty in the cyclization reaction in the presence of the furyl group even when starting from the saturated 1,4-diketone (Table 2, entry 14).[27] It should be noted that the *E*-isomers of **3b**, **3f**, and **3h** also afford the corresponding products **7b**, **7f**, and **7h** in 82–90% yields (Table 2, entries 4, 9, and 12). Therefore, it is unnecessary to separate the *Z*/*E* isomers before cyclization to the furans. It was interesting to find that the reaction of the diketone (*Z*)-**3*l*** under the above-noted standard conditions led to the undesired debrominated furan **7k** instead of **7*l*** in 70% yield. This is likely due to the known easy dehalogenation of 2-halogenated thiophenes in the presence of stannous chloride under acid conditions (Scheme 5).[28] In addition, the *Z*-isomers of the heterocoupling products **5** and **6** also afforded the desired products **8** and **9** in 82% and 80% yields, respectively (Scheme 6).

We also attempted to introduce a bromine atom into the newly synthesized trisubstituted furan ring **7**, to obtain the tetrasubstituted furan. The latter can be readily converted into related important derivatives via classic coupling reactions (Heck, Suzuki, Sonogashira, Liebeskind−Srogl, et al.). As shown in Scheme 7, treatment of 3-(methylthio)-2,5-diphenylfuran **7a** with bromine in chloroform at 0 °C within 5 min gave 3-bromo-4-(methylthio)-2,5-diphenylfuran **10a** in 92% yield (Table 3, entry 1). Bromo-furans **10b**, **10e**, and **10f** were also obtained in good yields from the corresponding furans (**7**) (Table 3, entries 4, 6, and 8). We were pleased to find also that the (*Z*)-**3a**, (*E*)-**3a**, (*Z*)-**3b**, (*Z*)-**3e**, and (*Z*)-**3f** could be converted directly into the corresponding bromo-furans **10** by means of 30% hydrogen bromide in chloroform (rather than in glacial acetic acid[25b]) at 0 °C in 58–64% yields (Table 3, entries 2, 3, 5, 7, and 9).

SCHEME 5



It has been reported that a number of 2,5-diaryl furans exhibit excellent biological activity.[29] Removal of the methylthio group may be achieved by treating the newly synthesized furan **7** with Raney Ni in ethanol.[30] This affords the 2,5-diaryl furans (**11**) in 85–91% isolated yields (Scheme 8 and Table 4).

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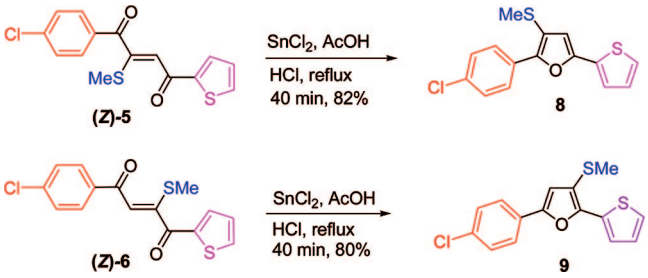
SCHEME 6



SCHEME 7

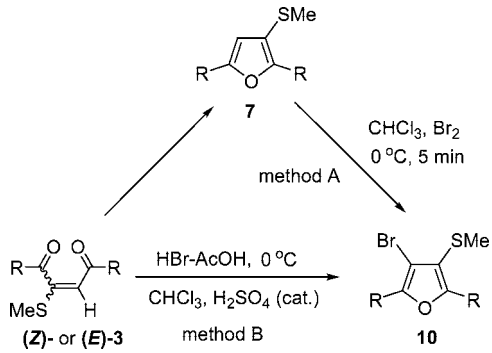


TABLE 3. Synthesis of 4-Bromo-3-(methylthio)-2,5-diaryl Furans

entry	reactants	R	method	products	yield[a] (%)
1	**7a**	C_6H_5	A	**10a**	92
2	(*Z*)-**3a**	C_6H_5	B	**10a**	61
3	(*E*)-**3a**	C_6H_5	B	**10a**	60
4	**7b**	4-MeC_6H_4	A	**10b**	90
5	(*Z*)-**3b**	4-MeC_6H_4	B	**10b**	60
6	**7e**	4-ClC_6H_4	A	**10e**	90
7	(*Z*)-**3e**	4-ClC_6H_4	B	**10e**	58
8	**7f**	4-BrC_6H_4	A	**10f**	88
9	(*Z*)-**3f**	4-BrC_6H_4	B	**10f**	64

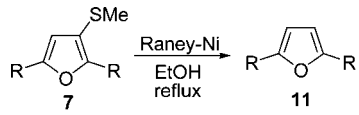
[a] Isolated yield.

TABLE 4. Reductive Desulfuration of 7 to 2,5-Diaryl Furan 11

entry	reactants	R	products	yield[a] (%)
1	**7a**	C_6H_5	**11a**	91
2	**7b**	4-MeC_6H_4	**11b**	85
3	**7d**	4-$EtOC_6H_4$	**11d**	89
4	**7e**	4-ClC_6H_4	**11e**	88
5	**7h**	1-naph	**11h**	85
6	**7i**	2-naph	**11i**	88
7	**7o**	2-benzofuryl	**11o**	90

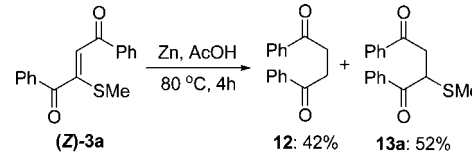
[a] Isolated yield.

SCHEME 8



With an efficient synthesis of substituted furan **7** in hand, we turned our attention to the preparation of the 3-methylthio-substituted pyrroles and thiophenes. We also expected to synthesize the pyrrole **14** from **3** through domino processes involving the reduction of the double bond followed by amination−cyclization. Proceeding according to the method reported by Rao and co-workers,[31] treatment of substrate (*Z*)-**3a** with ammonium formate (as a source of hydrogen and ammonia) in the presence of palladium on carbon (10%) in refluxing methanol led to a complicated mixture. Therefore an attempt was made to reduce the double bond selectively then isolate the saturated 1,4-diketone intermediate. Reaction of compound (*Z*)-**3a** with zinc dust in acetic acid at 80 °C for 4 h produced product **13a** in 52% yield along with the desulfurized product **12** in 42% yield (Scheme 9). Finally, stirring a solution of the *Z*- or *E*-isomer of **3a** in the presence of KI and concentrated hydrochloric acid in acetone at room temperature[32] gave saturated 1,4-diketone **13** in 71% and 70% yields, respectively, whose structure was confirmed by NMR spectroscopic and HRMS data. Furthermore, the structure of **13c** is supported by an X-ray crystal structure analysis (see the Supporting Information). Selective examples and yields are listed in Scheme 10 and Table 5. To our satisfaction, treatment of the saturated 1,4-diketones **13** with ammonium formate in refluxing acetic acid afforded 3-methylthio 2,5-diaryl-substituted pyrroles **14** in 80–92% yields. Similarly, treatment of **13** with Lawesson's reagent in refluxing toluene affords 3-methylthio-substituted thiophenes **15** in 75–88% yields along with desulfurized products **16** in 2–3% yields (Scheme 11 and Table 6).

SCHEME 9



SCHEME 10

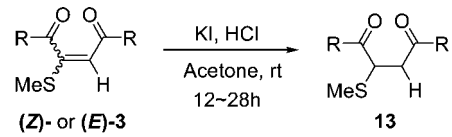


TABLE 5. Selective Reduction of the Double Bond in Diketones 3

entry	reactants	R	products	yield[a] (%)
1	(*Z*)-**3a**	C_6H_5	**13a**	71
2	(*E*)-**3a**	C_6H_5	**13a**	70
3	(*Z*)-**3b**	4-MeC_6H_4	**13b**	69
4	(*Z*)-**3c**	4-$MeOC_6H_4$	**13c**	73
5	(*Z*)-**3j**	2-furyl	**13j**	75
6	(*Z*)-**3n**	3-thienyl	**13n**	72
7	(*Z*)-**3o**	2-benzofuryl	**13o**	80

[a] Isolated yield.

Conclusion

In summary, we have developed a concise and efficient carbon−carbon bond-forming reaction from two sp^3-hybridized methyl groups. This is also a simple, effective, and interesting method for the synthesis of the important 1,4-diketones intermediates. Methylthio-substituted furans, pyrroles, and thiophenes and their related derivatives can be obtained in good yields via the Paal−Knorr cyclization of these 1,4-diketones. The cross-coupling reaction further confirms of the proposed self-sorting tandem reaction mechanism. This also offers the possibility of synthesis of a number of 1,4-diketones in one pot.

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SCHEME 11

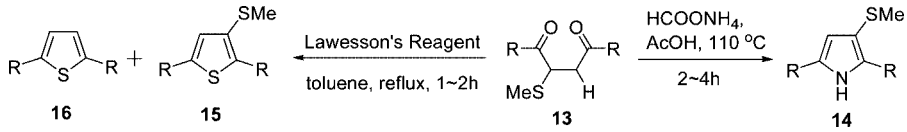

TABLE 6. Synthesis of 3-Methylthio-Substituted Pyrroles and Thiophenes

entry	reactants	R	products (isolated yield, %)		
1	**13a**	C_6H_5	**14a** (92)	**15a** (85)	**16a** (2)
2	**13b**	4-MeC_6H_4	**14b** (82)	**15b** (80)	**16b** (3)
3	**13c**	4-$MeOC_6H_4$	**14c** (88)	—[a]	—[a]
4	**13j**	2-furyl	—[b]	**15j** (75)	—[b]
5	**13n**	3-thienyl	**14n** (85)	—[a]	—[a]
6	**13o**	2-benzofuryl	**14o** (80)	**15o** (88)	**16o** (2)

[a] Not examined. [b] The desulfurized product was not isolated.

Experimental Section

Home-Coupling Reaction. Reference 21 and Supporting Information refer to the synthesis and characterization of 2-methylthio-substituted 1,4-diketones **3** of Table 1.

Cross-Coupling Reaction. A mixture of 4-chloroacetophenone (770 mg, 5 mmol), 2-acetylthiphene (630 mg, 5 mmol), iodine (5.08 g, 20 mmol), and CuO (2.40 g, 30 mmol) in DMSO (60 mL) was heated at 60–65 °C for 18 h. After filtration the reaction mixture was then poured into brine (150 mL) and the aqueous layer was extracted with $CHCl_3$ (4 × 40 mL). The extract was washed with 10% $Na_2S_2O_3$ then NaOH solution then dried over anhydrous Na_2SO_4, and after filtration solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (v/v = 12:1) as the eluent to give the mixture of the products **3k**, **5**, **6**, and **3e** in 67% overall yield. **(*Z*)-1-(4-Chlorophenyl)-2-(methylthio)-4-(2-thienyl)-2-butene-1,4-dione, (*Z*)-5:** 387 mg, yield 24%, mp 148–149 °C; IR (KBr) 3085, 1677, 1654, 1532, 1413, 1251, 1086, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.01 (d, J = 8.8 Hz, 2H), 7.66–7.63 (m, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.12 (dd, J_1 = 5.2 Hz, J_2 = 4.0 Hz, 1H), 6.90 (s, 1H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 190.4, 180.6, 159.2, 145.1, 141.5, 133.8, 133.1, 131.3, 131.1, 129.5, 128.2, 116.2, 15.4; EI-MS (70 eV) *m*/*z* (%) 308 (M − CH_3, 23), 306 (60), 256 (46), 231 (19), 139 (27), 110 (100); HRMS *m*/*z* calcd for $C_{15}H_{11}ClO_2S_2$ [M + H]$^+$ 322.9962, found 322.9961. **(*Z*)-4-(4-Chlorophenyl)-2-(methylthio)-1-(2-thienyl)-2-butene-1,4-dione, (*Z*)-6:** 97 mg, yield 6%, mp 102–103 °C; IR (KBr) 3104, 1650, 1633, 1534, 1406, 1241, 1088, 1035, 1008 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.89 (d, J = 8.8 Hz, 2H), 7.85 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.82 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.20 (dd, J_1 = 3.6 Hz, J_2 = 4.8 Hz, 1H), 7.14 (s, 1H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 186.8, 183.7, 160.6, 141.9, 139.1, 137.1, 136.5, 136.1, 129.4, 128.9, 115.9, 15.5; EI-MS (70 eV) *m*/*z* (%) 308 (M − CH_3, 29), 306 (100), 227 (16), 139 (33), 111 (38); HRMS *m*/*z* calcd for $C_{15}H_{11}ClO_2S_2$ [M + H]$^+$ 322.9962, found 322.9763.

General Procedure for the Synthesis of 3-Methylthio-2,5-diaryl Furans: 3-(Methylthio)-2,5-diphenylfuran (7a). A mixture of concentrated hydrochloric acid (4 mL) and acetic acid (6 mL) was heated to boiling, and stannous chloride (1.13 g, 5 mmol) was added, followed by (*Z*)-**3a** (141 mg, 0.5 mmol) in 5 mL of acetic acid. Heating was continued for 20 min then the reaction mixture was poured into 30 mL of water and extracted with $CHCl_3$ (3 × 15 mL). The organic layer was washed successively with saturated $NaHCO_3$ solution, and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography over silica gel with petroleum ether as the eluent to give **7a** (113 mg, yield 85%) as a pale yellow solid. Mp 35–36 °C; IR (KBr) 3059, 2986, 2918, 1604, 1488, 1443, 1056, 969 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.02 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.47–7.40 (m, 4H), 7.32–7.30 (m, 2H), 6.79 (s, 1H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 152.2, 149.1, 130.5, 130.0, 128.7, 128.4, 127.7, 127.2, 125.3, 123.7, 116.9, 109.5, 18.1; HRMS *m*/*z* calcd for $C_{17}H_{14}OS$ [M + H]$^+$ 267.0838, found 267.0826.

Furan **7a** was also obtained in 87% yield starting from (*E*)-**3a** under the same reaction conditions.

General Procedure for the Synthesis of 4-Bromo-3-(methylthio)-2,5-diarylfuran: 4-Bromo-3-(methylthio)-2,5-diphenylfuran (10a). Method A. To a solution of 1.33 g (5 mmol) of the furan **7a** in 15 mL of $CHCl_3$ was added 0.30 mL of bromine. After the reactant disappeared (TLC), the solvent was evaporated and the residue was purified by column chromatography over silica gel with petroleum ether as the eluent to give **10a** (1.13 g, 92%) as a white solid. Mp 79–80 °C; IR (KBr) 2916, 1483, 1443, 1121, 1069, 1032, 938, 767, 690, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.18 (d, J = 7.6 Hz, 2H), 8.06 (d, J = 7.6 Hz, 2H), 7.48–7.44 (m, 4H), 7.39–7.36 (m, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 152.8, 147.6, 129.7, 129.3, 128.5, 128.2, 126.1, 125.5, 116.8, 105.7, 18.7; EI-MS (70 eV) *m*/*z* (%) 346 (51), 344 (55), 265 (30), 237 (32), 221 (24), 145 (26), 105 (97), 77 (100); HRMS *m*/*z* calcd for $C_{17}H_{13}BrOS$ [M + H]$^+$ 344.9943, found 345.0250.

Method B. To a solution of (*Z*)-**3a** (282 mg, 1.0 mmol) in 8 mL of chloroform was added 1.0 mL of 30% hydrogen bromide in acetic acid at 0 °C. One drop of concentrated H_2SO_4 then was added to the mixture and stirring was continued overnight. The solvent was evaporated and the residue was purified by column chromatography over silica gel with petroleum ether as the eluent to give **10a** (210 mg, 61%). Furan **10a** was also obtained in 60% yield starting from (*E*)-**3a** under the same reaction conditions.

General Procedure for Reductive Removal of the Methylthio Group: 2,5-Bis(4-ethoxyphenyl)furan (11d). Compound **7d** (177 mg, 0.25 mmol) was dissolved in anhydrous EtOH (15 mL). Raney nickel (900 mg, excess) in EtOH was added, and the reaction mixture was refluxed for 1.5 h. The hot reaction mixture was filtered then washed with hot EtOH (15 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with petroleum ether as the eluent to give **11d** (137 mg, 89%) as a white solid. Mp 174–176 °C; IR (KBr) 2977, 2930, 1589, 1504, 1491, 1249, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.62 (d, J = 8.8 Hz, 4H), 6.92 (d, J = 8.8 Hz, 4H), 6.54 (s, 2H), 4.08 (q, J = 6.8 Hz, 4H), 1.43 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 158.3, 152.8, 125.0, 124.0, 114.7, 105.5, 63.5, 14.8; HRMS *m*/*z* calcd for $C_{20}H_{20}O_3$ [M + H]$^+$ 309.1485, found 309.1470.

Reduction of 2-Ene-1,4-diones to 1,4-Diones by Zn-AcOH. A mixture of (*Z*)-**3a** (141 mg, 0.50 mmol) and zinc dust (780 mg, 6.0 mmol) in acetic acid (15 mL) was stirred at 80 °C for 4 h until the reaction mixture became almost colorless. After filtration, the reaction mixture was poured into 20 mL of water and extracted with $CHCl_3$ (3 × 15 mL). The organic layer then was washed with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel with EtOAc/petroleum ether (v:v 1:10) as the eluent to give both the desulfurized byproduct **12** (43 mg, 42%) and **13a** (74 mg, 52%) as a white solid. **2-(Methylthio)-1,4-diphenylbut-1,4-dione (13a):** mp 98–101 °C; IR (KBr) 3428, 2919, 1665, 1637, 1594, 1325, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.09 (d, J = 8.0 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 7.61–7.46 (m, 6H), 4.87 (dd, J_1 = 10.0 Hz, J_2 = 4.0

Hz, 1H), 4.10 (dd, J_1 = 18.0 Hz, J_2 = 10.0 Hz, 1H), 3.44 (dd, J_1 = 18.0 Hz, J_2 = 4.0 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 197.6, 193.9, 136.1, 135.5, 133.5, 133.1, 128.6, 128.1, 40.8, 40.0, 11.8; HRMS *m*/*z* calcd for $C_{17}H_{16}O_2S$ $[M + H]^+$ 285.0944, found 285.0950.

Reduction of 2-Ene-1,4-diones to 1,4-Diones by KI-HCl. Potassium iodide (2.49 g, 15.0 mmol) and concentrated hydrochloric acid (15.0 mmol) were added to a stirred solution of diketone (*Z*)-**3a** (282 mg, 1.0 mmol) in acetone (100 mL) at room temperature. After 12 h the solvent was removed under reduced pressure, 10% $Na_2S_2O_3$ solution was added to the reddish residue, and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography over silica gel with EtOAc/petroleum ether (v:v = 1:10) as the eluent to give **13a** (202 mg, yield 71%). Compound **13a** was also obtained in 70% yield starting from (*E*)-**3a** under the same reaction conditions.

General Procedure for the Synthesis of 3-Methylthio Pyrroles: 3-(Methylthio)-2,5-diphenylpyrrole (14a). A solution of **13a** (142 mg, 0.50 mmol) in 12 mL of acetic acid was heated at 110 °C, then ammonium formate (945 mg, 15 mmol) was added. Heating was continued for 2 h and the cooled mixture was poured into 20 mL of water and extracted with $CHCl_3$ (3 × 10 mL). The organic layer then was washed with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel with petroleum ether as the eluent to give **14a** (122 mg, yield 92%) as a white solid. Mp 78–79 °C; IR (KBr) 3313, 1485, 1464, 1068, 762, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.47 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.49–7.35 (m, 6H), 7.30–7.21 (m, 2H), 6.62 (d, J = 2.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 132.2 (2C), 132.0, 131.8, 129.0, 128.7, 126.9, 126.7, 126.5, 123.7, 114.7, 110.9, 19.6; HRMS *m*/*z* calcd for $C_{17}H_{15}NS$ $[M + H]^+$ 266.0998, found 266.1001.

General Procedure for the Synthesis of 3-Methylthio Thiophenes: 3-(Methylthio)-2,5-diphenylthiophene (15a). To a toluene solution (15 mL) of **13a** (142 mg, 0.50 mmol) was added Lawesson's reagent (242 mg, 0.60 mmol). The mixture was stirred at reflux for 2 h. After being cooled to room temperature, the solvent was evaporated under reduced pressure, then the residue was purified by column chromatography on silica gel with petroleum ether as the eluent to give 3-(methylthio)-2,5-diphenylthiophene **15a** (120 mg, yield 85%) as a yellow oil together with desulfurized product **16a** (3 mg, 2%) as a white solid. **15a:** IR (KBr): 2920, 1597, 1484, 1451, 757, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.66 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.43–7.29 (m, 7H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 142.5, 138.6, 133.7, 133.6, 130.2, 128.9, 128.8, 128.4, 127.8, 127.7, 125.6, 125.5, 18.5; HRMS *m*/*z* calcd for $C_{17}H_{14}S_2$ $[M + H]^+$ 283.0610, found 283.0599.

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Supporting Information Available: The general experimental methods and the characterizing data for all other compounds, ^{1}H, ^{13}C NMR spectra for all new compounds, and X-ray crystallography data for compounds (*Z*)-**5**, **7b**, and **13c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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