JOC Note

A New Route to Multifunctionalized *p*-Terphenyls and Heteroaryl Analogues via [5C + 1C(N)] Annulation Strategy

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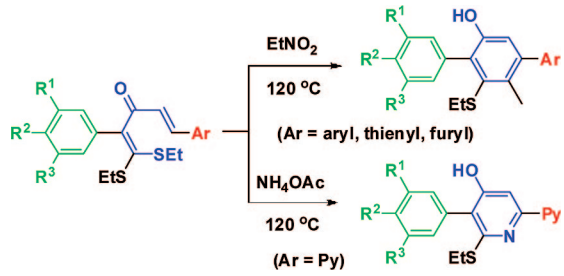

p-Terphenyls and heteroaryl analogues including bipyridines were prepared via [5C + 1C(N)] annulation of α-aryl-α-alkenoyl ketene-(*S*,*S*)-acetals (five carbon 1,5-bielectrophilic species) with nitroethane or ammonium acetate. The reaction features mild conditions, multisubstitution, and functional group tolerance and is metal catalyst free. The present protocol provides a new alternative to the conventional methodologies for the synthesis of teraryls.

p-Terphenyls have received considerable attention in the past decades, due to their presence as a structural motif in natural products, and their utility in biological and material sciences.[1] Naturally isolated *p*-terphenyl derivatives including terphenyllin, terferol, and terprenin have been reported to possess biological activities with potential therapeutic values.[2] Synthetic *p*-terphenyls are often exploited in the material areas such as molecular electronics, opto-electronics, chemical sensing and analysis, and photovoltaics because of their excellent photophysical properties.[3] There are two general methods that have been reported for the construction of teraryls. One is the transition metal-catalyzed aryl−aryl coupling reactions of the dihalobenzene derivatives with aryl nucleophiles (arylboronic acids, arylmagnesium bromides, and arylstannyl halides etc.).[4] The other is from diaryl-substituted open chain precursors to build up the central phenyl ring, for example, via transition metal-catalyzed [2 + 2 + 2] and [4 + 2] cycloadditions, which has been extensively reviewed.[5] For the former, the process is primarily limited by the availability of the organometallic coupling partners, and the incompatibility of the organometallic partners with some certain electrophilic functional groups (e.g., carbonyls, enones).[6] Although the latter approach is a common and valuable protocol to polysubstituted benzene and teraryl derivatives, the reaction often meets the problem of chemo- and regioselectivity. Therefore, to match the increasing scientific and practical demands, it is still of great importance to develop simple and efficient approaches for the construction of teraryls, especially those with flexible substitution patterns.

On the other hand, the utility of α-oxo ketene-(*S*,*S*)-acetals as versatile intermediates in organic synthesis has been recognized.[7] In our research on the chemistry of functionalized ketene-(*S*,*S*)-acetals,[8] easily available and structurally flexible α-alkenoyl ketene-(*S*,*S*)-acetals have been demonstrated as versatile building blocks for the efficient construction of a wide variety of six-membered carbo- and heterocycles including cyclohexenones (or phenols), 4-pyridones, and thiopyranones, on the basis of [5C + 1C],[9a] [5C + 1N],[9b,c] and [5C + 1S][9d] annulation

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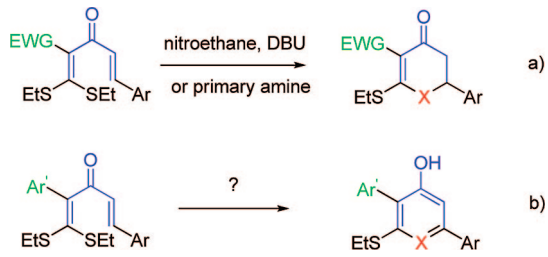
SCHEME 1

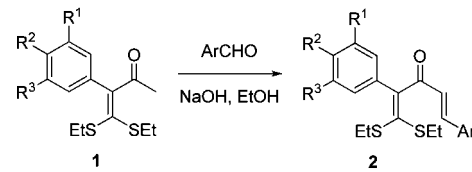


strategies, respectively (Scheme 1a).[9] Our continued interest in expanding the scope and potential applications of the formal [5 + 1] annulation strategy prompted us to explore the feasibility of construction of teraryls based on structurally modified α-aryl-α-alkenoyl ketene-(*S,S*)-acetals (Scheme 1b). To this end, α-phenyl-α-alkenoyl ketene-(*S,S*)-acetals were prepared and the [5 + 1] annulation reaction with nitroethane as a carbon nucleophile[10] and ammonium acetate as a nitrogen nucleophile were investigated, respectively. As a result, the teraryl frameworks including *p*-terphenyls and heteroaromatic analogues were successfully assembled via [5C + 1C(N)] annulation and subsequent aromatization. Thus, a concise, efficient, and flexible synthesis of unsymmetrical teraryls and analogues by this protocol was developed. The [5C + 1C(N)] annulation strategy employed here is versatile for both the phenyl- and pyridyl-cored teraryls and heteroaryl analogues. Furthermore, no problems of chemoselectivity and region-selectivity were involved in the explored reaction. Herein, we wish to report our experimental results.

The substrates 4,4-bis(ethylthio)-3-phenylbut-3-en-2-ones **1a** and **1b** were prepared via either our reported procedure (for **1a**) or the reaction of two molecules of 3-(bis(ethylthio)methylene)pentane-2,4-dione with NaOH as the base (for **1b**).[11] The condensation products **2** were prepared in 91−96% yields by treatment of **1** with a variety of aromatic aldehydes (Scheme 2), and were used directly without further purification.

With the easily available substrates **2** in hand, we started the [5C + 1C(N)] annulation reaction toward the synthesis of teraryl compounds. The [5C + 1C] reaction of **2** and nitroethane was examined first. A model reaction of **2a1** (1.0 mmol) and nitroethane (1.2 mmol) with DBU (4.0 mmol) as the base was carried out in DMF (10 mL) as reported previously in our group.[9] However, no reaction occurred when the mixture was stirred at either room temperature or heated to 70 °C. In view

SCHEME 2. The Aldol Condensation of 1a,b with Aldehydes



1 **2**

1a, **2a**: $R^1 = R^3 = H$; $R^2 = OMe$
1b, **2b**: $R^1 = OH$, $R^2 = COMe$, $R^3 = OEt$

of the different structure and thus different reactivity between α-aryl-α-alkenoyl ketene-(*S,S*)-acetals **2** and α-EWG-α-alkenoyl counterpart utilized before (as shown in Scheme 1), the reaction was further explored under elevated temperature. To our delight, when the mixture was stirred at 120 °C for 6.0 h, the above reaction proceeded smoothly and gave rise to the desired *p*-terphenyl compound **3a1** in 83% yield. Under the optimized conditions described above, a range of reactions between α-substituted phenyl-α-alkenoyl ketene-(*S,S*)-acetals **2a2**−**6** (1.0 mmol) and nitroethane (1.2 mmol) were carried out at 120 °C in DMF (10 mL), furnishing teraryls **3a2**−**6** in yields of 78−88% (Table 1, entries 2−6). Similarly, the reactions of substrates **2b** with nitroethane also gave satisfactory results (Table 1, entries 7−12). Compounds **3b1**−**7** were obtained in good to high yields (71−87%). In the teraryl or terheteroaryl products **3a1**−**6** and **3b1**−**7**, the Ar group varied from aryl (phenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-nitrophenyl) to heteroaryl (2-furyl, 2-thienyl, or 2-pyridyl). The heteroaryl anologues of *p*-terphenyls also represent an important class of organic molecules for their useful bio-, physio-, and pharmacological activities, as well as their application as organic materials.[3] One of the notable features of the teraryls and analogues **3** synthesized here is the multiple substituents and functional groups incorporated on the backbones (hydroxy, methyl, methoxy, ethoxy, ethylthio, acetyl, etc.), which provides the structural diversity of the unsymmetric teraryls and a potential for further modification. In addition, the mono- or diphenolic terphenyl frameworks have been found to exist widely in natural isolated terphenyl products.[1,2] Therefore, the present protocol gives a straightforward and general pathway to construct highly substituted teraryls and analogues of type **3** without the use of metal catalysts.

Pyridine is one of the most important nitrogen heterocycles, playing a key role in several biological processes.[12] Thus, the [5C + 1N] annulation reaction of **2** was investigated to construct teraryls with a central pyridine ring.[13] Initially, we focused on the synthesis of bipyridines, considering that it may act as a chelating ligand that forms complexes with most transition metal ions.[14] Thus, the mixture of **2a7** or **2b7** (Ar = 2-pyridyl) and

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(11) For synthetic details, please see the Supporting Information.

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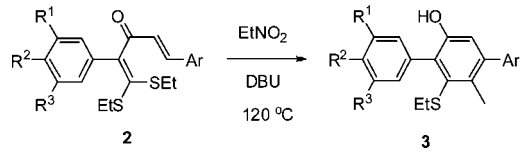
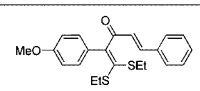
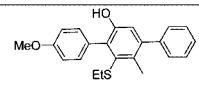
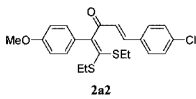
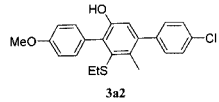
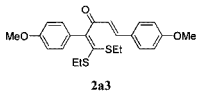
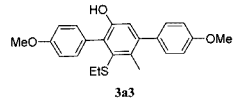
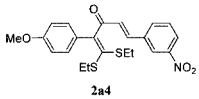
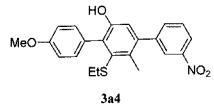
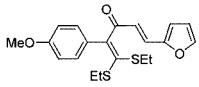
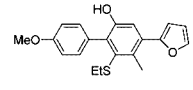
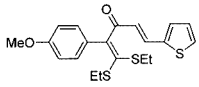
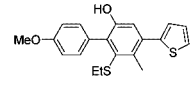
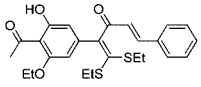
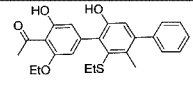
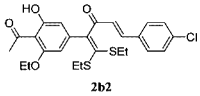
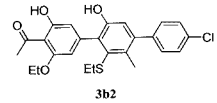
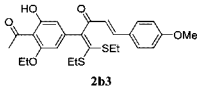
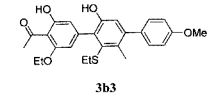
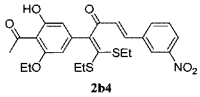
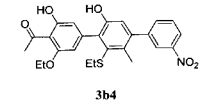
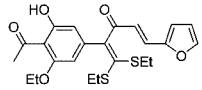
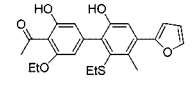
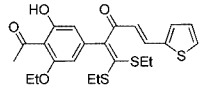
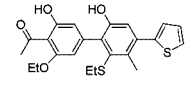
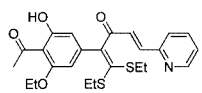
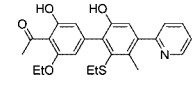
TABLE 1. Synthesis of *p*-Terphenyls and Their Heteroaryl Analogues Using [5C + 1C] Annulation

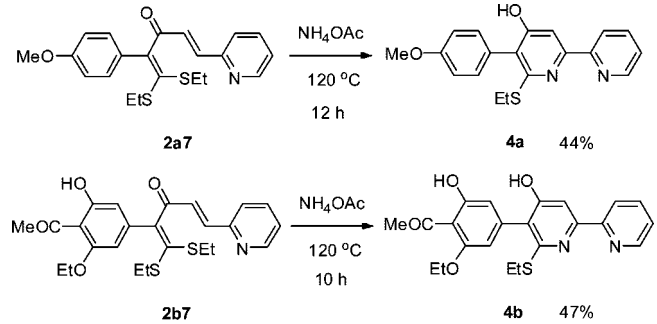


2 3

entry	substrate **2**	product **3**	yield[a] **3** (%)
1	 **2a1**	 **3a1**	83
2	 **2a2**	 **3a2**	88
3	 **2a3**	 **3a3**	80
4	 **2a4**	 **3a4**	78
5	 **2a5**	 **3a5**	83
6	 **2a6**	 **3a6**	87
7	 **2b1**	 **3b1**	80
8	 **2b2**	 **3b2**	85
9	 **2b3**	 **3b3**	84
10	 **2b4**	 **3b4**	71
11	 **2b5**	 **3b5**	74
12	 **2b6**	 **3b6**	87
13	 **2b7**	 **3b7**	71

[a] Reagents and conditions: **2** (1.0 mmol), $EtNO_2$ (1.2 mmol), DBU (4.0 mmol), DMF (10 mL), 120 °C, 6.0−8.0 h. [b] Isolated yield.

SCHEME 3. Synthesis of Multisubstituted Bipyridines Based on [5C + 1N] Annulation



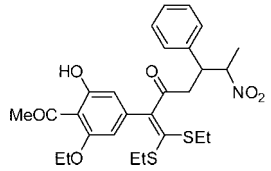
excess NH_4OAc (ammonia source,[15] 8.0 equiv) was stirred in DMSO at 120 °C for 10 h. Gratifyingly, 2,2′-bipyridines **4a** and **4b** were prepared by the one-pot procedure (Scheme 3), although the yields (44% for **4a** and 47% for **4b**) were incomparable to that of the teraryls produced by [5C + 1C] annulation (Table 1); it was noteworthy that the central pyridyl rings in compounds **4** could be formed via [5C + 1N] annulation and subsequent aromatization in formal dehydrogenation, most probably by air oxidation), while in our previous work on [5C + 1N] annulation reaction, the aza-cyclization products were demonstrated as pyridone derivatives, which could not further aromatize to give the pyridines.[9c] Similar dehydrogenation has been observed in our recent work[16a] and that reported by Xue et al.[16b] Clearly, 5-arylayed bipyridyls of type **4** may be constructed by the [5C + 1N] annulation protocol. In the following work to construct teraryls containing a central pyridine ring with other substrates like **2a1**, **2a4**, **2b1**, and **2b4**, however, the reactions were proved to be inefficient under otherwise identical conditions. It seems that the reactivity of **2** with various substrates is different and plays an important role in the [5C + 1N] annulation reaction.

In the reaction of substrate **2b** with nitroethane (Table 1, entry 7), a Michael adduct **5** was isolated in 53% yield by quenching the reaction within 3.0 h (Figure 1). On the basis of all above results, as well as our previous work,[9] a possible mechanism for the annulation of **2** with C/N nucleophiles is proposed, as depicted in Scheme 4. The tandem reaction led to teraryls and analogues involves Michael addition, intramolecular cyclization (addition−elimination), and aromatization sequences.

In summary, we have developed an efficient method for the synthesis of highly functionalized *p*-terphenyls and heteroaryl analogues using the [5C + 1C(N)] annulation reaction of α-aryl-α-alkenoyl ketene-(*S*,*S*)-acetal with carbon or nitrogen nucleophiles, which provides a new alternative route to the conventional metal-catalyzed methodologies. The reaction features mild conditions, multisubstitution, and functional group tolerance and is metal catalyst-free. Further work to construct diversely polysubstituted pyridines, bipyridines, and terpyridines is underway in our laboratory.

(15) Examples for the synthesis of pyridine derivatives using ammonium acetate as the nitrogen source, see:(a) Ladouceur, G. H.; Cook, J. H.; Doherty, E. M.; Schoen, W. R.; MacDougall, M. L.; Livingston, J. N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 461–464. (b) Rodriguez, H.; Suarez, M.; Perez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709–3712. (c) Bowman, M. D.; Jacobson, M. M.; Pujanauski, B. G.; Blackwell, H. E. *Tetrahedron* **2006**, *62*, 4715–4727.

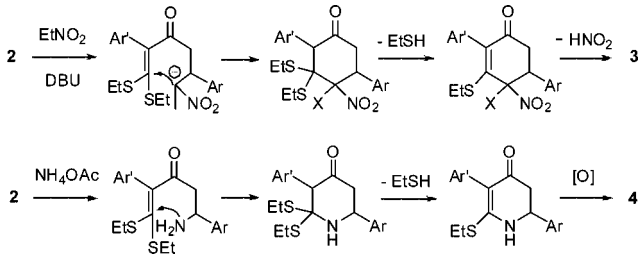
(16) Selected examples of aromatization via dehydrogenation, see: (a) Hu, J.; Zhang, Q.; Yuan, H.; Liu, Q. *J. Org. Chem.* **2008**, *73*, 2442–2445. (b) Xue, D.; Li, J.; Zhang, Z.-T.; Deng, J.-G. *J. Org. Chem.* **2007**, *72*, 5443–5445.



5

FIGURE 1. Structure of compound **5**.

SCHEME 4. Proposed Mechanism for the Formation of Teraryls and Their Derivatives



Experimental Section

General Procedure for Preparation of 3 (3a1 as an example). To a solution of 1,1-bis(ethylthio)-2-(4-methoxyphenyl)-5-phenylpenta-1,4-dien-3-one (**2a1**, 385 mg, 1.0 mmol) in DMF (10 mL) was added DBU (0.32 mL, 4.0 mmol) and nitroethane (0.17 mL, 1.2 mmol). The reaction mixture was heated to 120 °C for 6 h. After the starting material **2a1** was consumed as indicated by TLC, the resulting mixture was allowed to cool to room temperature. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether:diethyl ether = 4:1) to give **3a1** (290 mg, 83%) as a yellow solid.

4-Methoxy-6′-(ethylthio)-5′-methyl-*p*-terphenyl-2′-ol (3a1): mp 124−126 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, J = 7.5 Hz, 3H), 2.41 (s, 3H), 2.43−2.46 (m, 2H), 3.89 (s, 3H), 4.77 (s, 1H), 6.90 (s, 1H), 7.06 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.31−7.38 (m, 3H), 7.43 (d, J = 8.0 Hz, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.7, 19.4, 29.6, 55.3, 113.8, 114.5, 117.0, 127.0, 127.9, 128.2, 129.2, 131.88, 132.0, 134.8, 142.3, 143.4, 151.0, 159.4. Anal. Calcd for $C_{22}H_{22}O_2S$: C, 75.39; H, 6.33. Found: C, 75.40; H, 6.30.

General Procedure for the Preparation of 4 (4a as an example). To a solution of 1,1-bis(ethylthio)-2-(4-methoxyphenyl)-5-(pyridin-2-yl)penta-1,4-dien-3-one (**2a7**, 386 mg, 1.0 mmol) in DMSO (5 mL) was added NH_4OAc (616 mg, 8 mmol). The reaction mixture was heated to 100 °C for 10 h, then the resulting mixture was allowed to cool to room temperature. Next the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether:diethyl ether = 1:2) to give **4a** (149 mg, 44%) as a yellow solid.

6-(Ethylthio)-5-(4-methoxyphenyl)-2,2′-bipyridin-4-ol (4a): mp 114−116 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (t, J = 7.5 Hz, 3H), 3.20−3.24 (m, 2H), 3.87 (s, 3H), 4.00 (s, 1H), 7.04 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.32 (s, 1H), 7.57 (s, 1H), 7.81 (t, J = 8.0 Hz, 1H), 8.46 (d, J = 7.5 Hz, 1H), 8.64 (d, J = 4.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.9, 29.9, 55.5, 103.9, 115.1, 119.6, 121.2, 123.7, 126.4, 131.8, 137.0, 149.1, 151.3, 154.3, 156.6, 158.1, 159.9. IR (KBr, cm^{-1}) 686, 788, 1174, 1241, 1289, 1401, 1449, 1508, 1550, 1575, 1641, 2854, 2923, 2955. MS calcd m/z 338.4, found 339.5 $[(M + 1)]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.45; H, 5.38; N, 8.30.

Acknowledgment. Financial support of this research by NENU-STB07007 and the Department of Science and Technology of Jilin Province (20080421) is greatly acknowledged.

Supporting Information Available: Experimental details and characterization data for **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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