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Acetyltrimethylsilane: A Novel Reagent for the Transformation of 2*H*-Pyran-2-ones to Unsymmetrical Biaryls†

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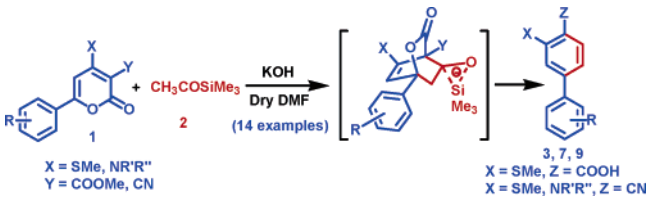
Received October 5, 2005



An expeditious synthesis of unsymmetrical biaryls functionalized with electron-withdrawing or -donating substituents is described and illustrated by carbanion-induced ring transformation of 2*H*-pyran-2-one using acetyltrimethylsilane (ATMS) as a novel reagent in good yield. The novelty of the reaction lies in the creation of an aromatic ring from 2*H*-pyran-2-ones via two-carbon insertion from ATMS used as a source of carbanion.

The significant advancements in the chemistry of organosilicon reagents over the past few decades have opened new avenues for their potential utility in regio- and stereochemical organic syntheses.[1] Among the various organosilicon reagents,[2] acyl silanes are of particular interest due to their reactive behavior and unusual physical and chemical properties associated with them. Chemically, alkanoyl- and benzoyl-alkyl/arylsilanes (R_3SiCOR'; R, R′ = alkyl, aryl) behave like classical ketones with some reagents, and their reactivity is quite different depending upon the substituents attached to them.[3] Although acyl silanes are being considered as poor substrates for functionalization due to high sensitivity toward basic conditions and light, they have been successfully used as synthetic equivalents of aldehydes provided with enhanced chemical stability and as useful intermediate for nucleophilic acylation reactions.[4] To the best of our knowledge, none have demonstrated synthetic utility in preparing functionalized biaryl compounds, which not only are the central building motifs of a large number of natural products[5] and synthetic pharmaceuticals but also are useful as versatile auxiliaries for asymmetric syntheses,[6] as chiral phases for chromatography,[7] and as important substrates for advanced materials.[8]

The regioselective palladium-catalyzed cross-coupling of organosilicon compounds with organic halides has been developed as a viable alternative to the cross-coupling of copper, magnesium, boron, tin, and zinc alkyls.[9] The most commonly used organosilicon reagent for the synthesis of symmetrical and unsymmetrical biaryls is aryl silane, which has been extensively studied by Hiyama and Hatanaka.[10] The cross-coupling of aryl(halo)silanes with aryl halides in the presence of a palladium catalyst is a general and practical route to symmetrical and unsymmetrical biaryls. Symmetrical biaryls have recently been prepared by Pd-catalyzed homocoupling of difluorosilanes in the presence of a dibromide as an oxidant.[11] Recently, phenyl(trialkoxy)silanes have been utilized to prepare functionalized biaryls via hypervalent silicate anion intermediate or by using palladium/imidazolium chloride system as a useful catalyst.[12] Despite their efficiency, the interest in aryl(halo/alkoxy)silane cross-coupling is limited by the difficulty of synthesizing such compounds. Additionally, non-palladium-catalyzed[13] reductive coupling reactions have been reported using either TTMSS-AIBN as promoters or in the presence of zinc dust and ammonium formate. Other organosilicon reagents such as silanols[14] and silacyclobutanes[15] were also proposed as useful reagents for biaryl synthesis in good to excellent yields. Nevertheless, the use of such reagents involves stoichiometric amounts of expensive activators or palladium catalysts.

The tremendous synthetic potential of organosilicon reagents in preparing regiospecifically substituted biaryls and difficulty in existing protocols prompted us to develop a new simple,

† CDRI Communication No. 6860.
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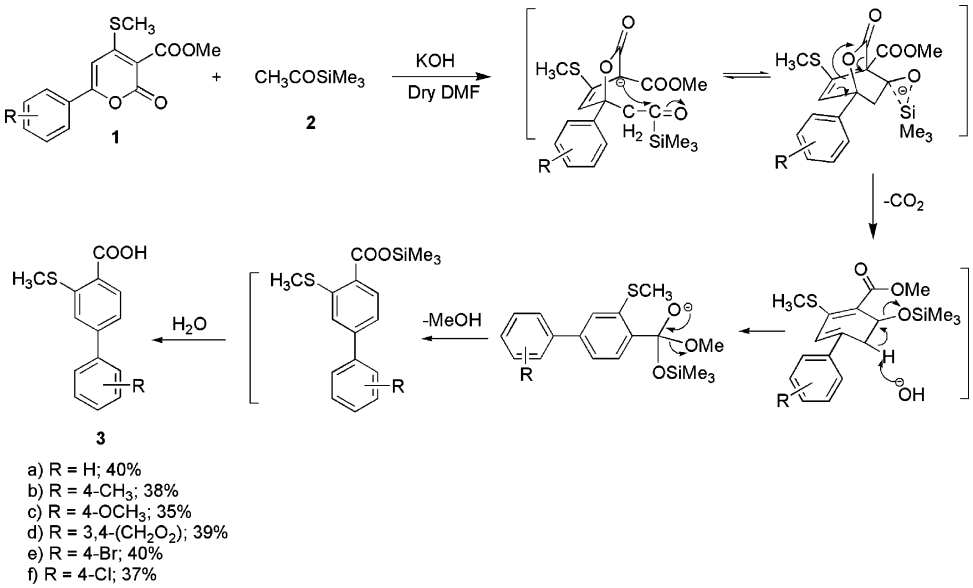
10.1021/jo052085y CCC: $33.50
Published on Web 12/22/2005

SCHEME 1



general, and inexpensive route for their synthesis. Herein we describe synthesis of functionalized biaryls from the reaction of aryllactones and acetyltrimethylsilane (ATMS) under mild basic conditions. The novelty of the procedure lies in the conversion of the 2*H*-pyran-2-one skeleton into an aromatic ring via two-carbon insertion using ATMS as a useful reagent.

Our synthetic approach to preparing functionalized biaryls **3a**−**f** is based on ring transformation of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl-2*H*-pyran-2-ones **1a**−**f** using ATMS as a carbanion source. The 2*H*-pyran-2-ones **1a**−**f** precursors have been prepared by the reaction of methyl 2-methoxycarbonyl-3,3-di(methylsulfanyl)acrylate with substituted acetophenones under alkaline conditions in high yields.[16] Lactones **1a**−**f** have three electrophilic centers: C2, C4, and C6 in which the latter is highly reactive toward nucleophiles due to the extended conjugation and the presence of the electron-withdrawing substituent at position 3 of the pyran ring. These biaryl compounds **3a**−**f** were synthesized by stirring an equimolar mixture of 2*H*-pyran-2-ones **1a**−**f**, ATMS, and powdered KOH in dry DMF under nitrogen atmosphere for 4−6 h at room temperature (Scheme 1). The reaction was performed in the dark to avoid decomposition of ATMS in light and was monitored by TLC, which showed a blue spot when exposed to short-wave UV radiation at 254 nm. After completion, the reaction mixture was poured into ice water and neutralized with dilute HCl. The crude product thus obtained was purified by silica gel chromatography. The ^{1}H NMR spectroscopic analysis of **3a** revealed one singlet at δ 2.49 for the SMe group, a doublet at 7.98 for an aromatic proton, and two doublets in the range of 7.72−7.54 for other aromatic protons. The absence of a methoxy proton signal in the range 3.8−4.2 and the presence of a carbonyl stretching peak at 1682 for aromatic carboxylic acid in IR spectrum revealed that the ester group is hydrolyzed to carboxylic acid under basic conditions. The molecular ion peak at *m*/*z* 258 allowed us to propose the structure for isolated compound as 3-methylsulfanyl-biphenyl-4-carboxylic acids **3a**−**f**. Finally, the structure of **3a** was confirmed by a single-crystal X-ray analysis (see Supporting Information).

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It was of interest to understand the mechanism of this hitherto unobserved type of reaction. It has been well-documented that acyl silanes are readily cleaved at room temperature by dilute aqueous base into silanol and aldehyde.[17] Although we carried out the reaction in dry DMF under inert atmosphere, there may be a possibility of hydrolysis of ATMS into acetaldehyde due to the presence of traces of water. To shed light on the reactive species (ATMS or acetaldehyde), we attempted the reaction in alcoholic alkaline condition by replacing the solvent from dry DMF to methanol, which should accelerate in situ formation of acetaldehyde, and thus should analogously yield the biaryls. However, this optimistic presumption was unsuccessful, and no biaryl product was obtained. It is also apparent that alkyl and aromatic groups attached to a silanoyl group dramatically influence the reactivity as well as the reaction products.[3] For example, when benzoyltriphenylsilanes are treated with diazomethane, two products (β-ketosilanes and the isomeric siloxyalkenes) are usually obtained in equal quantities. On the contrary, when acetyltriphenylsilanes are reacted with diazomethane, β-ketosilanes are obtained in major quantities.

After considering all the aspects, a plausible mechanism for the formation of a biaryl is depicted in Scheme 1. The transformation of 2*H*-pyran-2-one into a biaryl may proceed by enolate addition of ATMS at position C-6 of lactone **1**, followed by intramolecular cyclization involving the carbonyl functionality of ATMS and C-3 of the pyran ring to form a bicyclic intermediate. The intermediate after elimination of carbon dioxide formed an oxyanion, which on delocalization of negative charge can undergo silylcarbinol−alkoxysilane-type rearrangement, forming a silicon−oxygen bond, followed by elimination of siloxy group through a carbanionic intermediate. The resulting ester intermediate is smoothly transformed into the corresponding silylester, which on hydrolysis under mild basic conditions furnished a biaryl carboxylic acid (Scheme 1).

In addition to biaryls, heterobiaryls from heteroaryl−aryl couplings have found a unique place in various therapeutic areas

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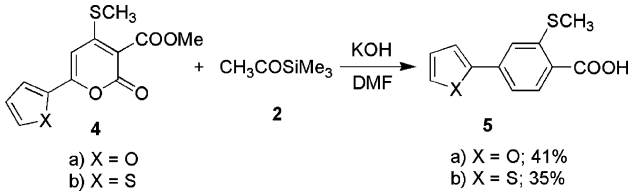
SCHEME 2



as well as in generating molecular devices.[9] Although the chemistry of heterobiaryls is replete with various palladium-catalyzed approaches, simple, inexpensive noncatalyzed methodologies are still nonexistent. Recently, an interesting route for preparing heterobiaryls has been developed by a straightforward anionic coupling of α-metalated heterocycles with halobenzene.[18] To demonstrate the utility of this route for preparing heterobiaryls, we carried out a reaction of 6-furyl/thienyl-3-methoxycarbonyl-4-methylsulfanyl-2*H*-pyran-2-one[16] (**4a**,**b**) with ATMS under the same reaction conditions (Scheme 2). After the usual workup, we isolated the compounds as 4-furan/thiophen-2-yl-2-methylsulfanylbenzoic acid **5a**,**b** in good yields.

To further expand the scope of this reaction, current interest focuses on fabricating useful biaryl building blocks by utilizing functionalized 2*H*-pyran-2-ones. Several studies[19,20] have demonstrated that the biaryl and teraryl synthons containing "cyano" functionality in their molecular framework dramatically influence the photophysical and electroluminescent properties of light emitting diode devices by lowering the energy of the LUMO, thus exhibiting a relatively low threshold voltage and high quantum efficiency. The paucity of the synthetic methodology for constructing a cyano group containing biaryls prompted us to exploit our methodology to prepare them.

The cyano group containing precursors, 6-aryl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles **6a**−**e**, were synthesized by reacting an equimolar mixture of methyl 2-cyano-3,3-di(methylsulfanyl)acrylate and substituted acetophenones in dry DMSO.[21] For ascertaining the course of reaction with these precursors, the 2*H*-pyran-2-ones **6a**−**c** were then reacted with ATMS in the presence of a base to furnish 3-methylsulfanylbiphenyl-4-carbonitriles **7a**−**c** in moderate yield as shown in Scheme 3. To achieve higher yields of biaryls, a series of optimization studies were carried out by varying reaction conditions and bases such as NaH, KOH, Et_3N, DIPA, K_2CO_3, LDA, DBU, and *t*-BuOK in suitable solvents. The potassium hydroxide in dry DMF under nitrogen atmosphere in dark was found to be the most appropriate. Unfortunately, our efforts to obtain the compounds in higher yields were not successful.

To prepare biaryls exclusively, we attempted to reduce the electrophilicity at position 4 of lactones **6a**−**e** by replacing the methyl sulfanyl group with a secondary amine such as piperidine. With this consideration, we prepared 6-aryl-2-oxo-4-piperidin-1-yl-2*H*-pyran-3-carbonitriles (**8a**−**e**) in high yields by refluxing a solution of lactone **6a**−**e** with piperidine in methanol for 6−8 h as described earlier.[21] The reaction of lactones **8a**−**e** and ATMS under the same reaction conditions as described in Scheme 1 gave 3-piperidin-1-ylbiphenyl-4-carbonitriles (**9a**−**e**) in good yields (Scheme 3). All the synthesized compounds were characterized by spectroscopic analyses.

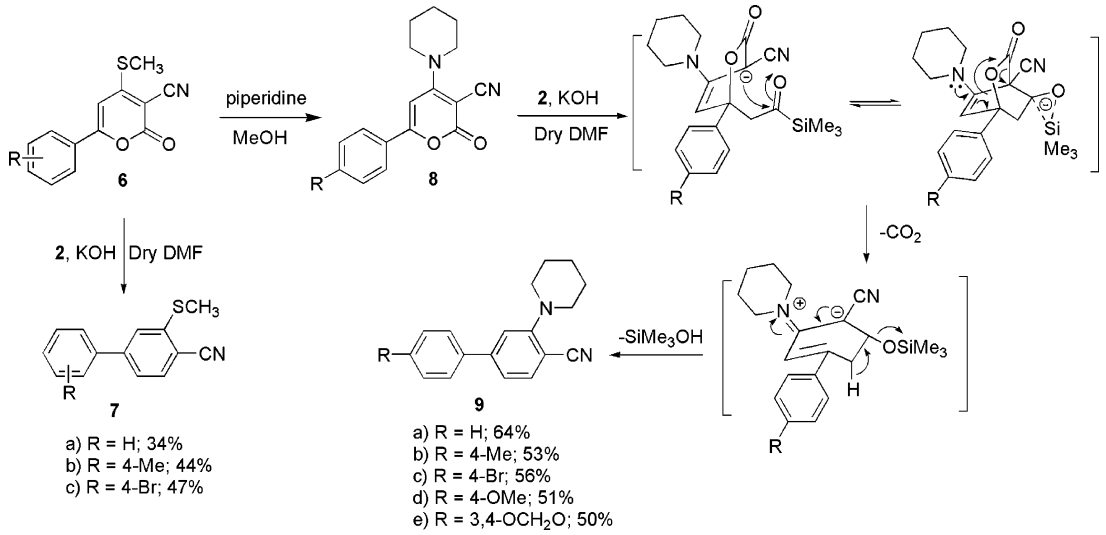
In summary, we have developed a new reagent acetyltrimethylsilane for the synthesis of unsymmetrical biaryls through carbanion-induced ring transformation of 2*H*-pyran-2-ones under mild basic conditions. This methodology is very simple, economical, and does not require expensive palladium catalysts that are normally used for C−C bond-forming reactions. The novelty of the reaction lies in the conversion of the lactone ring into an aromatic ring via two-carbon insertion involving the $-CH_2CO$ unit of the ATMS, in the presence of a base.

Experimental Section

The synthetic procedures and characterization data for all the new compounds are described in the Supporting Information. The data for one of the representative compounds from each scheme is described here. ATMS was purchased from a commercial supplier.

General Procedure for the Synthesis of 3a−e. A mixture of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl-2*H*-pyran-2-ones[16] **1** (1 mmol), acetyltrimethylsilane (**2**, 1.1 mmol), and powdered KOH (1.2 mmol) in dry DMF (5 mL) under dry nitrogen atmosphere was stirred at room temperature in the dark for 4−6 h. At the end, the reaction mixture was poured into ice water with vigorous stirring and finally neutralized with dilute HCl. The solid thus obtained was filtered, dried, and purified on a silica gel column using chloroform/hexane (3:1) as eluent.

SCHEME 3



3-Methylsulfanylbiphenyl-4-carboxylic Acid (3a): White solid; mp: 219−220 °C; MS (FAB): 244 (M^+); IR (KBr): 1680 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO-d_6) δ: 2.49 (s, 3H, SCH_3), 7.36−7.54 (m, 5H, ArH), 7.72−7.78 (m, 2H, ArH), 7.98 (d, 1H, J = 5.2 Hz, ArH), 13.01 (brs, 1H, COOH); Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.47; H, 5.08.

General Procedure for the Synthesis of 7a−c and 9a−e. A mixture of 6-aryl-4-methylsulfanyl/(piperidin-1-yl)-2-oxo-2*H*-pyran-3-carbonitrile[21] **6a−c** or **8a−e** (1 mmol), acetyltrimethylsilane (1 mmol), and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 6−8 h in the dark under dry nitrogen atmosphere. At the end, the reaction mixture was poured into ice water with vigorous stirring and finally neutralized with dilute HCl. The solid thus obtained was filtered and purified on a silica gel column using chloroform/hexane (1:9) as eluent.

3-Methylsulfanylbiphenyl-4-carbonitrile (7a): Light yellow solid; mp: 84−86 °C; MS (FAB): 226 ($M^+ + 1$); IR (KBr): 2221 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ: 2.62 (s, 3H, SCH_3), 7.36−7.70 (m, 8H, ArH); Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92. Found: C, 74.21; H, 4.99.

3-Piperidin-1-ylbiphenyl-4-carbonitrile (9a): Viscous oil; MS (FAB): 263 ($M^+ + 1$); IR (neat): 2220 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.60−1.68 (m, 2H, CH_2), 1.78−1.87 (m, 4H, $2CH_2$), 3.18−3.26 (m, 4H, $2CH_2$), 7.14−7.18 (m, 2H, ArH), 7.31−7.64 (m, 6H, ArH); Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92. Found: C, 82.26; H, 6.78.

Acknowledgment. This work was supported by the Department of Science and Technology (DST), New Delhi, India. We are thankful to RSIC, CDRI, Lucknow, for providing spectroscopic analyses of the synthesized compounds.

Supporting Information Available: Complete experimental details and characterization data of all new compounds (**3a−f**, **6b**, **7a−c**, **8a−e**, **9a−e**). A copy of ^1H NMR spectra of all the new compounds. X-ray structure and packing diagrams of compound **3a** including noncovalent interactions studies. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052085Y

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