

Regioselective synthesis of functionally hindered α -methylstyrenes through ring transformation of 2*H*-pyran-2-ones with mesityl oxide[#]

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Abstract—A regioselective synthesis of α -methylstyrenes with electron-withdrawing or -donating substituents is described and illustrated by carbanion-induced ring transformation of 2*H*-pyran-2-one with mesityl oxide in excellent yield. The potential of the reaction lies in the creation of an aromatic ring possessing an isopropenyl unit from six membered-lactones at room temperature under mild reaction conditions.

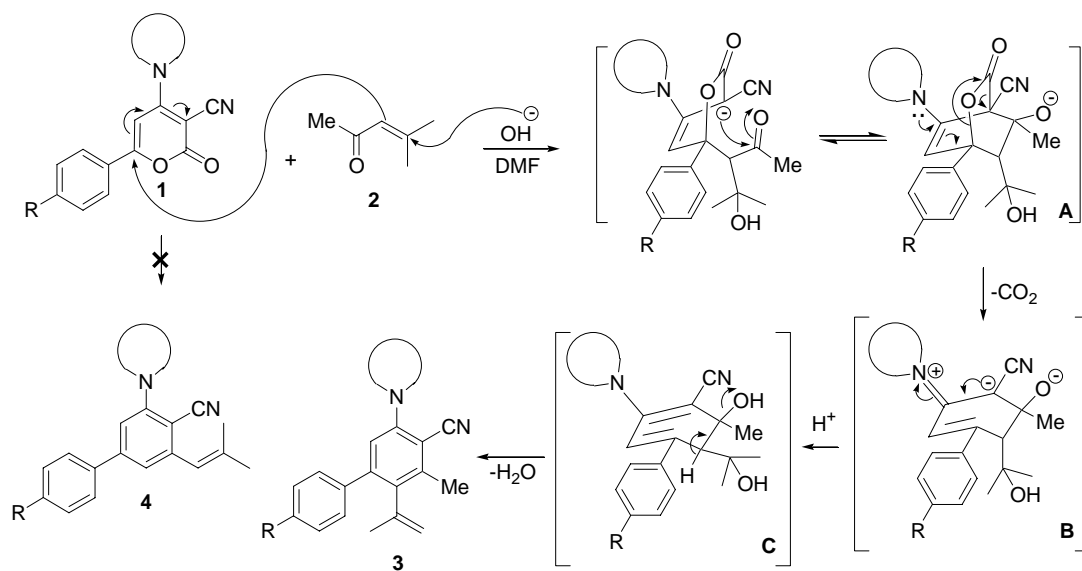
Styrene units are synthetically useful intermediates in olefin metathesis as well as in the formation of new polymeric materials. These structural motifs are frequently derived from naturally occurring terpenes such as piquerol A.^{1,2} Natural products having styrene scaffolds in isolated or rigid conformations have been reported to possess interesting biological activities.³ In addition, these scaffolds are fascinating and challenging research objectives in order to explore their intrinsic photophysical and photochemical properties.⁴

Numerous synthetic methodologies are available for the synthesis of styrenes, which involve the ring-opening of phenylcyclopropanes by treatment with Lochmann's base,⁵ catalytic dehydration of dimethyl-*o*-xenylcarbinol in the vapour phase,⁶ aromatization of piquerol A using Pd/C (5%) as catalyst,¹ 1,5-sigmatropic hydrogen rearrangement of 5-ethylidene-methylene-cyclohexa-1,3-diene derivatives⁷ and by *retro*-Diels-Alder⁸ reaction of 6-amino-2-imino-4-methyl-7-phenylbicyclo[2.2.2]-5-octene-1,3,3,5-tetracarbonitrile. The construction of styrenes can also be achieved by transition metal-catalyzed cross-coupling reaction of potassium vinyltrifluoroborates with arenediazonium compounds in the presence of an azapalladacycle complex at room temperature using an ionic liquid as the reaction medium.⁹ Functionally congested styrenes have been prepared by the cross coupling reactions of aryl halides and potassium vinyltrifluoroborates in the presence of Pd-catalysts

in moderate yields.^{10,11} However, the procedure suffers from the requirement of excess reagent, long reaction times and/or the formation of reduced byproducts. Molander and co-workers¹² developed improved protocols for the synthesis of functionalised styrenes using potassium vinyltrifluoroborates and aryl or heteroaryl halides as coupling partners in the presence of 2 mol% PdCl₂ and 6 mol% PPh₃ as a catalyst system in THF/H₂O with CsCO₃ as the base.

Despite the wide synthetic potential of these metal-assisted cross-coupling reactions for the synthesis of hindered styrene systems, they suffer from the requirements for expensive organometallic reagents/catalysts, harsh reaction conditions and formation of undesired byproducts. Thus, there exists a need to develop an expedient route for the synthesis of functionally hindered styrene systems that does not require specialized reagents or catalysts and which could offer an economical general route with the flexibility of introducing electron donor or acceptor groups into their molecular architecture.

Herein, we report a new protocol for the synthesis of functionalized styrene based biaryls in high yields through ring transformation of 2*H*-pyran-2-ones with mesityl oxide. The strength of the procedure lies in the creation of a benzene ring substituted with an isopropenyl unit utilizing a simple ring transformation strategy without using an organometallic reagent or catalyst.



Entry	Structure	Reaction time (h)	Yield (%)
3a		17	65
3b		14	72
3c		16	80
3d		16	72
3e		18	77
3f		17	61
3g		18	79

Scheme 1. Synthesis of α -methylstyrene derivatives **3a-g**

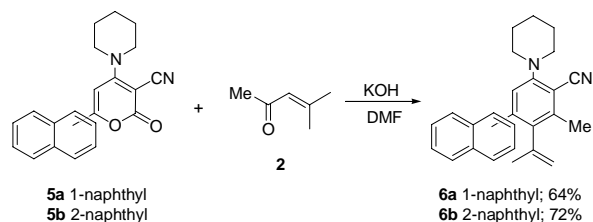
During our recent studies on 2*H*-pyran-2-ones, we developed new methodologies for the synthesis of functionally congested benzenes,¹³ 1,2-di-, 1,2,3-tri- and 1,2,3,4-tetraarylbenzenes¹⁴ and various heterocyclic compounds such as pyridines,¹⁵ pyridinones,¹⁶ isoquinolines,¹⁷ benzothiophenes¹⁸ and benzofurans¹⁹ through nucleophile-induced ring transformation reactions. The 2*H*-pyran-2-one ring system of **1a-g** possesses three electrophilic centres; C-2, C-4 and C-6 in which C-6 is highly prone to nucleophilic attack due to the extended conjugation and the presence of the electron withdrawing substituent at position 3 of the pyranone ring.

The 2*H*-pyran-2-ones²⁰ **1a-g** were conveniently prepared in high yields by the reaction of 2-cyano-3,3-bis-(methylsulfanyl)-acrylic acid methyl ester with acetophenones under alkaline conditions, followed by reaction with secondary amines. The synthesis of functionalized styrenes **3a-g** was achieved by stirring an equimolar mixture of 2*H*-pyran-2-one **1a-g**, mesityl oxide **2** and powdered KOH in DMF for 14-18 h at room temperature (Scheme 1). The reaction was monitored by TLC and on completion was poured into ice water and neutralized with dilute HCl. The crude product thus obtained was filtered and purified on a silica gel column using 25% chloroform in hexane as eluent. The ¹H NMR spectrum of **3a** showed five sharp singlets at 1.60 (3H), 2.52 (3H), 4.84 (1H), 5.23 (1H) and 6.76 (1H) ppm for the protons of two methyl groups, two geminal protons of a methylene group and an aromatic proton, respectively. Three multiplets for the piperidine ring protons and a multiplet at 7.29-7.43 ppm for five aromatic protons were in agreement with the proposed structure of **3a**. A nitrile peak at 2213 cm⁻¹ in the IR spectrum and a molecular ion peak *m/z* at 317 in the ESI mass spectrum corroborated the presence of the target 2-isopropenyl-3-methyl-5-piperidin-1-yl-biphenyl-4-carbonitrile **3a**. The structure of **3a** was unambiguously confirmed by HRMS analysis. The ¹H NMR spectrum of the product ruled out the possibility of 5-(2-methyl-propenyl)-3-piperidin-1-yl-biphenyl-4-carbonitrile **4a** being the product. Similarly, all the other synthesized compounds **3b-g** were characterized by spectroscopic analysis.²¹

The transformation of 6-aryl-4-amine-1-yl-2*H*-pyran-2-ones **1a-g** into styrene biaryls **3a-g** is possibly initiated by Michael addition of the anion generated from mesityl oxide at C6 of lactone **1**,

followed by intramolecular cyclization involving the carbonyl functionality of **2** and C3 of the pyranone ring to form intermediate **A**. This intermediate on elimination of carbon dioxide, followed by protonation and dehydration furnished products **3a-g** in moderate to good yields.

A benzene ring substituted with bulky naphthyl moieties exists as conformational or configurational stereoisomers depending on the extent of steric hindrance around the biaryl axis.²² The rigid binaphthyl skeleton has a rather high-energy barrier to atropisomerization and thus can be isolated in enantiopure forms.²³ Several 2,2'-substituted-1,1'-binaphthyls are used widely as chiral ligands or as auxiliaries for various asymmetric syntheses.



Scheme 2.

In order to demonstrate the utility of this approach in preparing sterically hindered biaryls, we prepared 6-naphthyl-2*H*-pyran-2-ones **5a,b** by stirring a mixture of methyl 2-cyano-3,3-dimethylsulfanyl-acrylate with 1- or 2-acetonaphthone in DMSO in the presence of a base as described earlier.^{14,20} The reaction of **5a,b** with mesityl oxide **2** in the presence of powdered KOH in dry DMF analogously furnished 3-isopropenyl-2-methyl-4-naphthalen-1/2-yl-6-piperidin-1-yl-benzonitriles **6a,b** in good yields (Scheme 2). The formation of naphthylstyrenes at room temperature indicates that the electronic and steric properties of the substituents did not affect the reaction pathway.

In summary, we have prepared functionally hindered styrene biaryls through carbanion-induced ring transformation of functionalized 2*H*-pyran-2-ones in moderate to good yields. Due to the mild reaction conditions under which the ring transformation occurs, this protocol can be applied in the presence of various functional groups. This methodology may be applicable to the synthesis of hindered biaryl systems. Further applications of our 'lactone methodology' for the synthesis of functionally hindered styrene systems are currently in progress.

Acknowledgements

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 - General procedure for the synthesis of 3a-g and 6a,b:** A mixture of 6-aryl-4-amine-1-yl-2H-pyran-2-one **1** or **5** (1 mmol), mesityl oxide (1.2 mmol) and powdered KOH (1.5 mmol) in dry DMF (5 mL) was stirred at room temperature for 14-18 h. On completion 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 (1:4) as eluent; **3a**: white solid; mp 112-114 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.60 (s, 3H, CH₃), 1.61-1.71 (m, 2H, CH₂), 1.74-1.85 (m, 4H, 2CH₂), 2.52 (s, 3H, CH₃), 3.11-3.19 (m, 4H, 2CH₂), 4.84 (s, 1H, CH), 5.23 (s, 1H, CH), 6.76 (s, 1H, ArH), 7.29-7.43 (m, 5H, ArH); ¹³C (50.0 MHz, CDCl₃) δ 19.55, 24.53, 24.60, 26.61, 53.86, 107.11, 114.22, 118.41, 119.00, 127.74, 128.15, 129.34, 132.51, 136.50, 141.13, 142.22, 143.00, 156.18; IR (KBr) 2213.4 cm⁻¹ (CN); MS (ESI) 317 (M⁺+1); HRMS calcd for C₂₂H₂₄N₂: 316.1940, found: 316.1930. **3c**: white solid; mp 140-142 °C; ¹H NMR (200 MHz, CDCl₃) δ 1.56-1.61 (m, 5H, CH₂ & CH₃), 1.74-1.80 (m, 4H, 2CH₂), 2.49 (s, 3H, CH₃), 3.09-3.17 (m, 4H, 2CH₂), 4.82 (s, 1H, CH), 5.23 (s, 1H, CH), 6.89 (s, 1H, ArH), 7.20 (d, J = 8.4 Hz, 2H, ArH), 7.28 (d, J = 8.4 Hz, 2H, ArH); ¹³C (50.5 MHz, CDCl₃) δ 19.53, 24.49, 24.67, 26.58, 53.82, 118.09, 119.34, 122.09, 129.21, 131.01, 131.36, 132.43, 136.19, 140.57, 141.36, 142.75, 144.16, 156.23; IR (KBr) 2191 cm⁻¹ (CN); MS (ESI) 395 - ⁷⁹Br + H⁺, 397 - ⁸¹Br + H⁺; HRMS calcd for C₂₂H₂₃BrN₂: 394.1045, found: 394.1038. **6b**: white solid; mp 122-124 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.56-1.70 (m, 5H, CH₂ & CH₃), 1.76-1.84 (m, 4H, 2CH₂), 2.53 (s, 3H, CH₃), 3.12-3.19 (m, 4H, 2CH₂), 4.88 (s, 1H, CH), 5.20 (s, 1H, CH), 6.83 (s, 1H, ArH), 7.44-7.53 (m, 3H, ArH), 7.75-7.84 (m, 4H, ArH); ¹³C (75.5 MHz, CDCl₃) δ 17.88, 22.85, 23.02, 24.94, 52.19, 105.45, 116.73, 116.97, 117.47, 124.90, 125.00, 125.92, 125.98, 126.40, 126.48, 126.80, 131.19, 131.59, 134.91, 137.62, 139.54, 141.32, 143.78, 154.53; IR (KBr) 2218 cm⁻¹ (CN); MS (ESI) 367 (M⁺+1); HRMS calcd for C₂₆H₂₆N₂: 366.2096, found: 366.2108.
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