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Synthesis of *o*,*m*-cymene-cored biaryls through a carbanion-induced ring transformation strategy☆

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Abstract—Aromatic compounds derived from two or more 'isoprene units' are the core structures found in several natural products of biological importance. Among them, cymene derivatives are of particular interest due to the unique structural and biological properties associated with them. In this letter, we describe an expeditious synthesis of cymene-cored unsymmetrical biaryls functionalized with donor and acceptor substituents prepared in excellent yields by the carbanion-induced ring transformation of 2*H*-pyran-2-ones with ketones.

Benzene scaffolds functionalized with methyl and isopropyl functionalities in flexible or rigid conformations are encountered in many natural products[1] (terpenoids such as *o*,*m*,*p*-cymene) as well as in synthetic pharmaceuticals.[2] Several of the biaryls, in which one of the aryl rings is substituted with one or more isopropyl units, have recently been reported as potent glucagon receptor antagonists for the treatment of diabetes.[3] The biaryl, Bay-27-9955 functionalized with two isopropyl units has been reported to inhibit glucagon from the human glucagon receptor with an IC_{50} value of 110 nM.[4] The compound was found to be orally active with a bioavailability of 40% and a half-life of 11–17 h in male rats and was selected for advanced clinical trials.[5] In addition, several 1,3-diisopropylbenzene-based imidazolium salts are used as chiral auxiliaries for a variety of asymmetric catalysis processes.[6] Recently, Buchwald's chiral biaryl phosphine ligands with triisopropyl moieties (XPhos and *tert*-butyl Xphos) have emerged as versatile chiral ligands for palladium-catalyzed asymmetric syntheses.[7] Therefore, the necessity for an efficient and concise synthesis of biaryls having desired functionalities is important in natural product chemistry as well as in the discovery of new reagents for asymmetric synthesis.

The aryl–aryl bond formation for the preparation of symmetrical and unsymmetrical biaryls is one of the most useful and important tools in modern organic chemistry. The construction of biaryls can be achieved either by intermolecular or by intramolecular cross-coupling of two similar or dissimilar aromatic rings in the presence of organo-metal complexes. Palladium-catalyzed cross-coupling reactions between electrophilic compounds, Ar-X (X being mainly Cl, Br, I and OTf) and organometallic species Ar-M (M being Mg, Zn, Sn and B) are versatile procedures for the construction of biaryl systems. The asymmetric version can be accomplished by the use of chiral reagents or auxiliaries and a plethora of examples are available in the literature.[8] Generally, the preparation of these compounds is based on the Pd-mediated Suzuki–Miyaura coupling procedure, which has been frequently used to prepare a wide array of biaryl scaffolds. Despite the wide synthetic potential of these metal-assisted cross-coupling reactions, they suffer from the requirements for expensive organometallic reagents/catalysts, harsh reaction conditions and undesired by-products. Thus, there exists a need to develop an expedient route for the synthesis of biaryls that does not require specialized reagents or catalysts and which could offer an economical general route with flexibility for introducing electron donor or acceptor groups.

Herein, we report a new route for the synthesis of functionalized biaryls through a ring transformation reaction of 2*H*-pyran-2-ones with either 2-methyl-pentan-3-one or substituted phenyl acetones in high yields.

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This approach has obvious advantages over metal-assisted aryl–aryl coupling since molecular diversity can be generated utilizing a simple transformation strategy with desired conformational flexibility around the biaryl axis, and a limited use of expensive organometallic reagents, and/or tolerance of various functional groups.

The precursor 2*H*-pyran-2-ones **1a**–**f** were conveniently prepared in high yields by the reaction of methyl 2-cyano-3,3-dimethylsulfanylacrylate[9] with substituted acetophenones under alkaline conditions, followed by reaction with secondary amines. Lactones **1a**–**f** possess three electrophilic centres; C2, C4 and C6 in which the latter position is highly susceptible to nucleophilic attack due to the extended conjugation and the presence of the electron-withdrawing substituent at position 3 of the pyran ring. Our approach to preparing functionalized biaryls **3a**–**f** was based on the ring transformation of 6-aryl-2*H*-pyran-2-ones **1a**–**f** using 2-methylpentan-3-one **2** as a carbanion source. The synthesis of **3a**–**f** was achieved by stirring an equimolar mixture of 2*H*-pyran-2-ones **1a**–**f**, 2-methylpentan-3-one and powdered KOH in DMF for 10–12 h at room temperature (Scheme 1, Table 1). The reaction was monitored by TLC and upon completion was poured into ice water and neutralized with dilute HCl. The crude product thus obtained was filtered and purified on a neutral alumina column using 25% chloroform in hexane as an eluent.

The transformation of 6-aryl-2*H*-pyran-2-ones into biaryls is possibly initiated by attack of the carbanion generated from 2-methylpentan-3-one at position C6 of lactones **1a**–**f**, followed by intramolecular cyclization involving the carbonyl functionality of **2** and C3 of the pyranone ring and then elimination of carbon dioxide, followed by protonation and dehydration to yield **3a**–**f** in good yields.

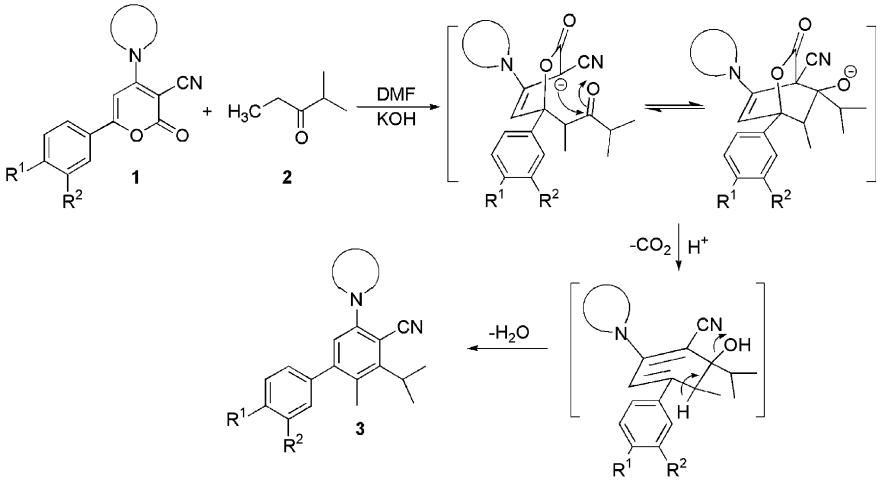
It is worth mentioning that the biaryl compounds **3a**–**f** with adjacent methyl and isopropyl moieties can be considered as derivatives of *ortho*-cymene. The literature on the preparation of *ortho*-cymenes shows a paucity of references. They are very difficult to prepare by conventional approaches and are thus very expensive (Aldrich Cat. No. 25527-0: *ortho*-cymene: 500 mg, approx. $200.00).

Table 1.

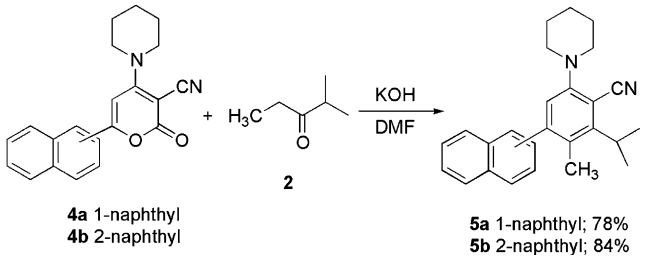
Product	R^1	R^2	N	Yield (%)
3a	Br	H	Piperidine	88
3b	Cl	H	4-Methylpiperidine	87
3c	Cl	H	4-Phenylpiperazine	91
3d	F	H	Piperidine	79
3e	OMe	H	Piperidine	84
3f	3,4-CH_2O_2		4-Phenylpiperazine	86

A benzene ring substituted with bulky naphthyl moieties exists as conformational or configurational stereoisomers depending on the extent of steric hindrance involved around the biaryl axis.[10] The rigid binaphthyl skeleton has a rather high-energy barrier to atropisomerization and thus can be isolated as the enantiopure species.[11] Several 2,2′-substituted-1,1′-binaphthyls are widely used as chiral ligands or as auxiliaries for various asymmetric syntheses. In order to demonstrate the utility of this approach in preparing sterically hindered biaryls, we prepared 6-naphthyl-2*H*-pyran-2-ones (**4a**,**b**) by stirring a mixture of methyl 2-cyano-3,3-dimethylsulfanylacrylate with 1- or 2-acetonaphthone in the presence of a base in DMSO, as described earlier.[9] The reaction of **4a**,**b** with 2-methylpentan-3-one **2** in the presence of powdered KOH in dry DMF furnished 2-isopropyl-3-methyl-4-naphthyl-6-piperidin-1-yl-benzonitriles **5a**,**b** in good yields (Scheme 2).

The reaction was further exploited for the synthesis of *meta*-cymene derivatives, which are also very expensive and difficult to prepare by classical approaches. To obtain compounds with methyl and isopropyl moieties around the biaryl axis, the key lactone, 6-isopropyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile **8** was prepared in a 60% yield by reacting an equimolar mixture of ketene dithioacetal **6** with 3-methylbutan-2-one **7** in the presence of KOH in dry DMSO. The meth-



Scheme 1.

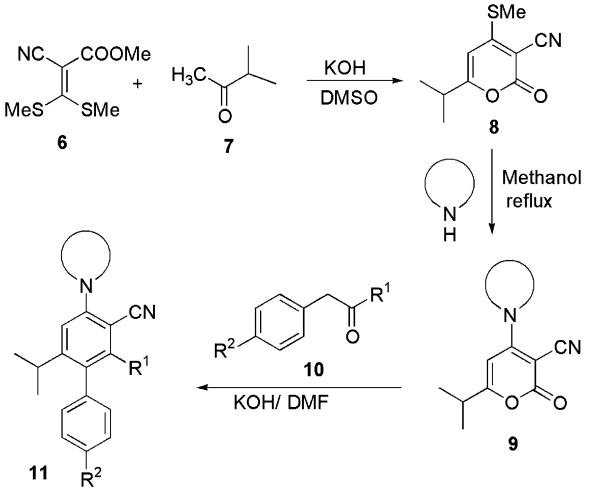


Scheme 2.

ylsulfanyl group of **8** was replaced by different secondary amines to reduce the electrophilicity at position 4 of lactone **8** and thus to avoid undesired side reactions. 6-Isopropyl-2*H*-pyran-2-ones **9a**,**b** were prepared in high yields by refluxing a solution of lactone **8** with either one equivalent of 4-phenylpiperazine or piperidine in methanol for 6–8 h (Scheme 3). The isopropyl-based biaryls **11** were synthesized in excellent yields by stirring a mixture of 2*H*-pyran-2-ones **9a**,**b** with substituted ketones **10** in the presence of a base. All the compounds prepared were characterized by spectroscopic analysis.[12,13]

These compounds are similar to the Buchwald catalysts (XPhos and *tert*-butyl XPhos) but with the advantage of having an electron donor or acceptor groups in their molecular architecture, which can be utilized for the development of new ligands with an improved catalytic activity.

In summary, we have prepared functionally demanding biaryls through the carbanion-induced ring transformation of functionalized 2*H*-pyran-2-ones in excellent 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 and development of new biaryl ligands for asymmetric synthesis. Further applications of our 'lactone methodology' in the synthesis of hindered biaryl systems are currently in progress.



11	Amine	R^1	R^2	Yield (%)
a	4-phenylpiperazine	*i*-Pr	H	82
b	4-phenylpiperazine	Me	OMe	84
c	piperidine	Me	OMe	84

Scheme 3.

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12. *General procedure for the synthesis of* **3a**–**f** *and* **5a**,**b**: A mixture of 6-aryl-2*H*-pyran-2-one **1a**–**f** or **4a**,**b** (1 mmol), 2-methylpentan-3-one (1.2 mmol) and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 10–12 h. The reaction mixture was poured into ice water with vigorous stirring and neutralized with dilute HCl. The solid thus obtained was filtered and purified on a neutral alumina column using chloroform–hexane (1:4) as an eluent. Compound **3a**: white solid; mp 162–164 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (d, $J = 7.2$ Hz, 6H, $2CH_3$), 1.54–1.58 (m, 2H, CH_2), 1.74–1.80 (m, 4H, $2CH_2$), 2.13 (s, 3H, CH_3), 3.00–3.10 (m, 4H, $2CH_2$), 3.48–3.64 (m, 1H, CH), 6.69 (s, 1H, ArH), 7.12 (d,

$J = 8.2$ Hz, 2H, ArH), 7.55 (d, $J = 8.2$ Hz, 2H, ArH); IR (KBr) 2214 cm^{-1} (CN); MS (FAB) 397 (M^++1); HRMS calculated for $C_{22}H_{25}BrN_2$ 396.12011, found: 396.12043. Compound **3b**: white solid; mp 160–162 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (d, $J = 4.8$ Hz, 3H, CH_3), 1.49 (d, $J = 7.2$ Hz, 6H, $2CH_3$), 1.55–1.59 (m, 2H, CH_2), 1.70–1.78 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.62–2.76 (m, 2H, CH_2), 3.39–3.60 (m, 2H, CH and CH_2), 6.70 (s, 1H, ArH), 7.18 (d, $J = 8.4$ Hz, 2H, ArH), 7.40 (d, $J = 8.4$ Hz, 2H, ArH); IR (KBr) 2206 cm^{-1} (CN); MS (FAB) 367 (M^++1); HRMS calculated for $C_{23}H_{27}ClN_2$ 366.18628, found: 366.18649; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.08, 20.72, 21.82, 30.62, 31.31, 34.54, 53.28, 105.61, 118.40, 127.10, 128.45, 130.23, 133.45, 140.51, 146.68, 152.11, 156.24. Compound **5b**: white solid; mp 158–160 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (d, $J = 7.2$ Hz, 6H, $2CH_3$), 1.54–1.60 (m, 2H, CH_2), 1.74–1.83 (m, 4H, $2CH_2$), 2.18 (s, 3H, CH_3), 3.02–3.13 (m, 4H, $2CH_2$), 3.52–3.73 (m, 1H, CH), 6.83 (s, 1H, ArH), 7.38 (d, $J = 8.4$ Hz, 1H, ArH), 7.48–7.56 (m, 2H, ArH), 7.71 (s, 1H, ArH), 7.82–7.93 (m, 3H, ArH); IR (KBr) 2211 cm^{-1} (CN); MS (FAB) 368 (M^+); HRMS calculated for $C_{26}H_{28}N_2$ 368.22525, found: 368.22509; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.24, 20.78, 24.14, 26.30, 31.17, 54.02, 99.99, 105.45, 118.56, 118.74, 126.25, 126.49, 127.20, 127.44, 127.54, 127.75, 128.01, 132.45, 133.17, 139.70, 147.94, 152.00, 156.52.

13. *General procedure for the synthesis of* **11a**–**c**: A mixture of 6-isopropyl-4-*sec*.amino-2-oxo-2*H*-pyran-3-carbonitrile **9** (1 mmol), ketone **10** (1.2 mmol) and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 8–12 h. The reaction mixture was poured into ice water with vigorous stirring and neutralized with dilute HCl. The solid thus obtained was filtered and purified on a neutral alumina column using chloroform–hexane (1:4) as an eluent. Compound **11a**: white solid; mp 190–192 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, $J = 6.8$ Hz, 6H, $2CH_3$), 1.32 (d, $J = 6.8$ Hz, 6H, $2CH_3$), 2.53–2.64 (m, 1H, CH), 2.82–2.93 (m, 1H, CH), 3.37–3.48 (m, 8H, $4CH_2$), 6.84–6.94 (m, 3H, ArH), 6.98–7.04 (m, 2H, ArH), 7.05–7.21 (m, 2H, ArH), 7.37–7.46 (m, 4H, ArH); IR (KBr) 2216 cm^{-1} (CN); MS (FAB) 423 (M^+). Compound **11c:** white solid; mp 168–170 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, $J = 6.8$ Hz, 6H, $2CH_3$), 1.61–1.68 (m, 2H, CH_2), 1.76–1.83 (m, 4H, $2CH_2$), 2.16 (s, 3H, CH_3), 2.66–2.77 (m, 1H, CH), 3.12–3.21 (m, 4H, $2CH_2$), 3.86 (s, 3H, OCH_3), 6.83 (s, 1H, ArH), 6.90–7.04 (m, 4H, ArH); IR (KBr) 2207 cm^{-1} (CN); MS (FAB) 349 (M^++1); HRMS calculated for $C_{23}H_{28}N_2O$ 348.22017, found: 348.22162.