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Regioselective synthesis of functionally congested biaryls through a novel C–C bond formation reaction☆

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Abstract—An expeditious synthesis of unsymmetrical biaryls functionalized with electron-withdrawing or -donating substituents is described and illustrated by the carbanion-induced ring transformation of 2*H*-pyran-2-ones with malononitrile in excellent yields.

Biaryl ring systems functionalized with electron donor or acceptor moieties are not only the central motifs of a large number of natural products[1] and synthetic pharmaceuticals but are also useful as versatile auxiliaries for asymmetric syntheses,[2] as chiral phases for chromatography[3] and as important substrates for chiral liquid crystalline materials.[4]

While the chemistry of symmetrical and unsymmetrical biaryls is replete with synthetic methods, most of them fall into the categories of the inter- and intramolecular cross coupling of two aromatic rings in the presence of organometallic complexes. Reductive dimerization of aryl halides is one of the oldest methods[5] for the construction of biaryls using copper bronze as a reducing agent. Oxidative coupling of electron-rich aromatic phenols also leads to the formation of biaryls in moderate yields.[6] Recently, palladium-catalyzed cross coupling between the electrophilic compounds Ar–X (X being mainly Br, I and OTf) and organometallic species Ar–M (M being Mg, Zn, Sn and B) has become increasingly popular for the construction of symmetrical and unsymmetrical biaryl ring systems.[7] Among them, the palladium-catalyzed aryl-boronic acid coupling (Suzuki reaction) has become a general and versatile route to access functionalized biaryls due to the commercial availability of several aryl-boronic acids, easy work-up and tolerance of the reaction to aqueous media. Despite the broad synthetic applicability of the Suzuki reaction, the expansion of these methods to prepare functionally congested biaryls places constraints on the choice of reagents, catalysts and/or reaction conditions. Therefore, the necessity for an efficient and concise synthesis of biaryls having functional group diversity is evident in natural product chemistry as well as in the discovery of new reagents for asymmetric synthesis.

Herein, we report an efficient and convenient procedure for the preparation of functionally congested biaryls through the reaction of ethyl 2-cyano-3,3-di(methylsulfanyl)acrylate with either aryl acetones or propiophenones followed by a base-catalyzed ring transformation of 2*H*-pyran-2-ones **3** with malononitrile. The beauty of the procedure lies in the creation of a functionally crowded aryl ring through lactonization without using an organometallic reagent or a catalyst.

Our approach to prepare functionalized biaryls **5a**–**e** is based on the ring transformation of 5-aryl-3-cyano-6-methyl-4-methylsulfanyl-2*H*-pyran-2-ones **3a**–**e** by using malononitrile as a carbanion source. The 2*H*-pyran-2-ones **3a**–**e** used as parent precursors were prepared by the reaction of ethyl 2-cyano-3,3-di(methylsulfanyl)acrylate[8,9] **1** with substituted aryl acetones **2a**–**e** under alkaline conditions in high yields (Scheme 1). Lactones, **3a**–**e** have three electrophilic centres; C2, C4 and C6 in which the latter is highly reactive towards nucleophiles due to extended conjugation and the presence of the electron withdrawing substitutent at position 3 of the pyran ring. The biaryl compounds **5a**–**e** were

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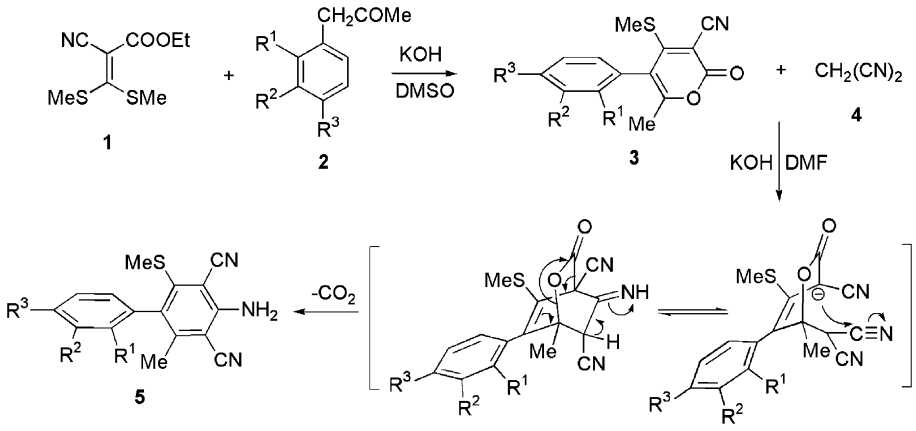


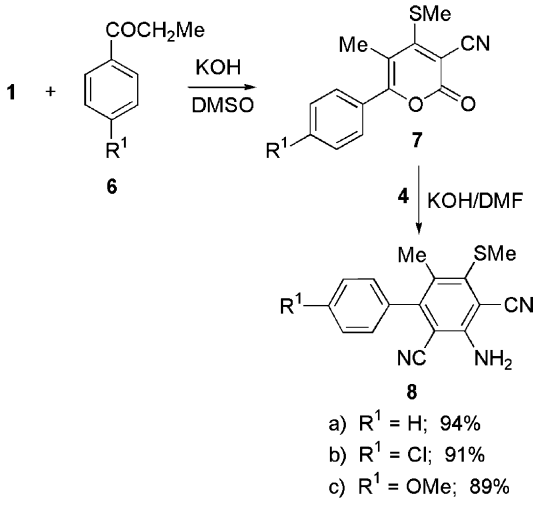
Entry	R^1	R^2	R^3	Yield (%)	
				3	5
a	F	H	H	78	94
b	H	H	F	82	87
c	H	H	CF_3	81	90
d	OMe	H	OMe	79	89
e	H	OMe	OMe	84	91

Scheme 1.

synthesized by stirring an equimolar mixture of 2*H*-pyran-2-ones **3a**–**e**, malononitrile and powdered KOH in DMF for 12–15 h at room temperature (Scheme 1). The reaction was monitored by TLC and thereafter poured into ice water and neutralized with dilute HCl. The crude product thus obtained was purified by silica gel chromatography and characterized by elemental and spectroscopic analyses.[10]

The transformation of 5-aryl-2*H*-pyran-2-ones into biaryls is possibly initiated by attack of the malononitrile carbanion at position C-6 of lactone **3**, followed by intramolecular cyclization involving one of the nitrile functionalities and C-3 of the pyranone ring and elimination of carbon dioxide to yield **5a**–**e**.

The reaction was further exploited by reacting an equimolar mixture of ketene dithioacetal **1** with propiophenones **6** in dry DMSO to prepare 5-methyl-4-methylsulfanyl-2-oxo-6-phenyl-2*H*-pyran-3-carbonitriles **7a**–**c** in 80–90% yields (Scheme 2). The 2*H*-pyran-2-ones **7a**–**c** were then reacted with malononitrile in the presence of a base to afford 3-amino-6-methyl-5-methylsulfanyl-biphenyl-2,4-dicarbonitriles **8a**–**c** in 89–94% yields.



Scheme 2.

In summary, we have prepared functionally congested biaryls through the carbanion-induced ring transformation of functionalized 2*H*-pyran-2-ones in excellent yields. This methodology may be applicable to the synthesis of other complex biaryls, which are difficult to prepare by classical cross coupling procedures.

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9. General procedure for the synthesis of compound **3**: a mixture of ethyl 2-cyano-3,3-di(methylsulfanyl)acrylate **1** (10 mmol), aryl acetone (11 mmol) and powdered KOH (12 mmol) in dry DMSO (50 mL) was stirred at room temperature for 10 h. After completion, the reaction mixture was poured into ice water with constant stirring. The precipitate thus obtained was filtered and purified on a silica gel column using chloroform as eluent. Compound **3c**: yellow solid; yield 81%; mp 142–144 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (s, 3H, CH_3), 2.85 (s, 3H, SCH_3), 7.42 (d, 1H, $J = 7.5$ Hz, ArH), 7.49 (s, 1H, ArH), 7.63 (t, 1H, $J = 7.6$ Hz, ArH), 7.75 (d, 1H, $J = 7.6$ Hz, ArH); IR (KBr) 1692 (CO), 2212 cm^{-1} (CN); MS (FAB) 326 (M^++1). Anal. Calcd for $C_{15}H_{10}F_3NO_2S$: C, 55.38; H, 3.10; N, 4.31. Found: C, 55.49; H, 3.13; N, 4.26.
10. General procedure for the synthesis of compound **5**: a mixture of 5-aryl-3-cyano-6-methyl-4-methylsulfanyl-2*H*-pyran-2-one **3** (1 mmol), malononitrile (1 mmol) and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 12–15 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 and purified on a silica gel column using chloroform–hexane (1:2) as eluent. Compound **5a**: white solid; yield 94%; mp 192–194 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.30 (s, 3H, SCH_3), 5.22 (br s, 2H, NH_2), 7.04–7.19 (m, 4H, ArH); IR (KBr) 2220 (CN), 3352 (NH), 3413 cm^{-1} (NH); MS (FAB) 298 (M^++1). Anal. Calcd for $C_{16}H_{12}FN_3S$: C, 64.63; H, 4.07; N, 14.13. Found: C, 64.69; H, 4.10; N, 14.19. Compound **8a**: white solid; yield 94%; mp 220–222 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.16 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 5.12 (br s, 2H, NH_2), 7.20–7.25 (m, 2H, ArH), 7.47–7.50 (m, 3H, ArH); IR (KBr) 2221 (CN), 3348 (NH), 3407 cm^{-1}(NH); MS (FAB) 280 (M^++1). Anal. Calcd for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N, 15.04. Found: C, 68.88; H, 4.78; N, 15.16.