Regioselective Synthesis of Functionally Crowded Benzenes at Room Temperature through Ring Transformation of 2*H*-Pyran-2-ones[1]

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Abstract: An expeditious synthesis of highly substituted benzenes with electron-withdrawing or electron-donating substituents is described and illustrated by carbanion-induced ring transformation of 2*H*-pyran-2-one with malononitrile in excellent yield. The novelty of the reaction lies in the creation of an aromatic ring at room temperature from a six-membered lactone under mild reaction conditions.

Key words: 2*H*-pyran-2-one, benzene, malononitrile, ring transformation reaction

Benzene compounds functionalized with electron-donor or -acceptor substituents such as alkyl, alkoxy, amino, nitrile or ester groups are useful scaffolds in organic synthesis, and are widely used in industry as well as in the laboratory. In particular, the synthesis of highly functionalized benzenes in a regioselective manner is one of the challenging tasks in academic endeavours.[2] Direct substitutions onto the benzene scaffolds by electrophilic or nucleophilic substitution reactions,[3] metal-catalyzed coupling reactions[4] and metalation–functionalization reactions[5] offer a versatile approach to the synthesis of a plethora of di- and trisubstituted benzene analogues, but some of them suffer from low positional selectivity of electron-donating or -withdrawing groups and/or from orienting effects of the substituents when applied to the synthesis of highly hindered aromatic systems. Substantial improvements and developments in metal-catalyzed cross-coupling reactions have been made in recent years, which furnish congested benzene derivatives in a regioselective manner.[6] Other general regioselective methods for the synthesis of functionalized benzenes include directed *ortho*-metalation reactions,[7] Ir-catalyzed selective borylation of arenes and heteroarenes at the positions *ortho* with respect to cyano groups,[8] Suzuki–Miyaura couplings of hindered substrates using Buchwald's catalyst[9] or in the presence of a bioxazoline-derived nitrogen–heterocyclic carbene ligand.[10]

Numerous alternative synthetic protocols that build up aromatic moiety from acyclic precursors[11] have received a great deal of attention for the preparation of highly functionalized benzene derivatives. The construction of benzene skeleton from acylic precursors include benzannulation reactions such as [3+2+1]-Dötz reaction of Fisher carbene complexes,[12] Danheiser alkyne–cyclobutenone cyclization,[13][4+2]-cycloaddition of metalacyclopentadienes and alkynes,[14] [2+2+2]- and [4+2]-cycloaddition reactions in the presence of transition-metal catalyst,[15] [4+2]-Yamamoto benzannulation of O-alkynyl benzaldehyde and alkyne,[16] [4+2]-annulation of Baylis–Hillman adducts[17] and [3+3]-cyclocondensation between bielectrophiles and binucleophiles.[18] Although these benzannulation approaches afford a wide variety of aromatic compounds, the utilization of these protocols for the preparation of functionally congested benzenes such as substituted isophthalonitriles places constraints on the choice of reagents or conditions. Aromatic compounds with nitrile and amine functionalities not only possess interesting biological activities[19] but are also useful synthons for their transformation to quinazolines[20] and fluorenones.[21] Although numerous regio- and stereoselective Diels–Alder reactions[22] of 2*H*-pyran-2-ones with electron-deficient and electron-rich dienophiles do provide benzene derivatives, they require forcing thermal reaction conditions to eliminate the carbon dioxide from the adduct and/or are associated with a mixture of positional isomers. The wide-ranging applications and limitations of existing protocols prompted us to develop a simple, general and efficient route that could offer flexibility of substituent variations on benzene scaffold.

Herein we report an efficient and convenient procedure for the synthesis of highly functionalized benzene derivatives through the reaction of methyl 2-cyano-3,3-dimethylsulfanylacrylate with substituted acetones followed by base-catalyzed ring transformation of 2*H*-pyran-2-ones using malononitrile as a source of carbanion. The advantage of the procedure lies in the creation of functionalized benzenes generated through lactonization at room temperature without using an organometallic reagent or a catalyst.

The chemistry of 2*H*-pyran-2-one derivatives is very interesting, which find diverse synthetic applications as a diene component in Diels–Alder reactions. During our recent studies on 2*H*-pyran-2-ones, we developed new protocols for the synthesis of pyridines,[23] pyridones,[24] dibenzofurans,[25] and biaryls[26] through nucleophile-induced ring transformation reactions. The topology of 2*H*-pyran-2-one ring system in **3a**–**e** is characterized by the presence of three electrophilic centers; C-2, C-4 and C-6 in which C-6 position is highly prone to nucleophiles due to the extended conjugation and the presence of the

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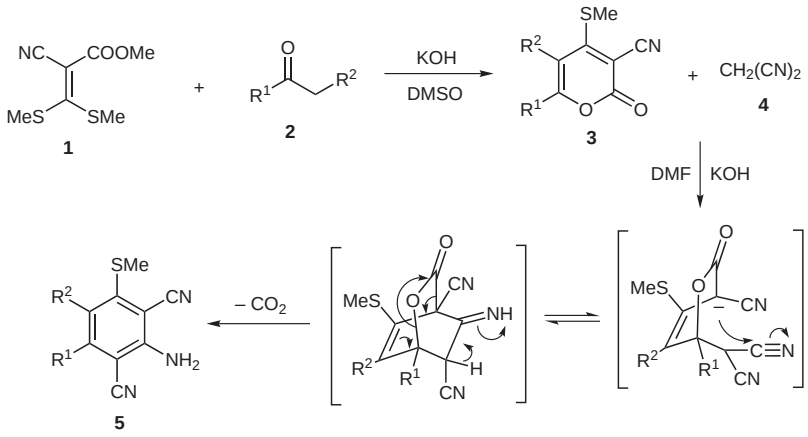
electron-withdrawing substituent at position 3 of the pyranone ring. Our synthetic approach to preparing highly substituted benzenes **5a**–**e** is based on ring transformation of 2*H*-pyran-2-ones **3a**–**e** by using malononitrile as a carbanion source. The 2*H*-pyran-2-ones **3a**–**e** used as a parent precursor were prepared by the reaction of methyl 2-cyano-3,3-dimethylsulfanylacrylate[27] (**1**) with substituted acetones **2a**–**e** under alkaline conditions in high yields (Table 1). The highly functionalized benzene derivatives **5a**–**e** were synthesized by stirring an equimolar mixture of 2*H*-pyran-2-ones **3a**–**e**, malononitrile and powdered KOH in DMF for 8–12 hours at room temperature (Table 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 on neutral alumina column using chloroform–hexane (1:9) as eluent and characterized by spectroscopic analyses.[28]

A plausible reaction mechanism for the formation of highly functionalized benzenes **5a**–**e** is based on Michael–Ziegler–Thorpe–retro-Diels–Alder-type reaction of **1** with active methylene compound under mild reaction conditions as depicted in Table 1. The reaction is initiated by the Michael addition of an anion, generated from a molecule of substituted acetones **2**, to the ketene-*S*,*S*-acetal **1** followed by intra-molecular cyclization to form a

Table 1 Synthesis of Highly Functionalized Benzene Derivatives **5a**–**e**



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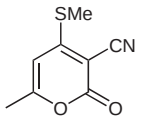
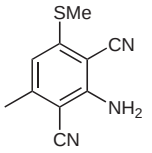
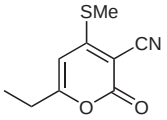
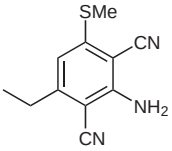
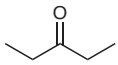
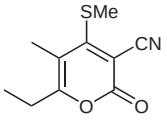
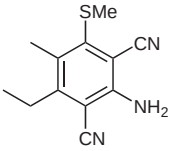
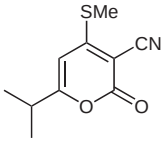
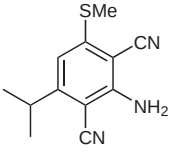
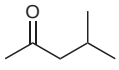
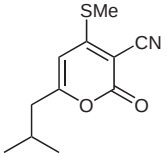
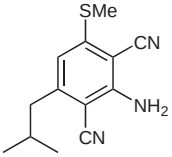
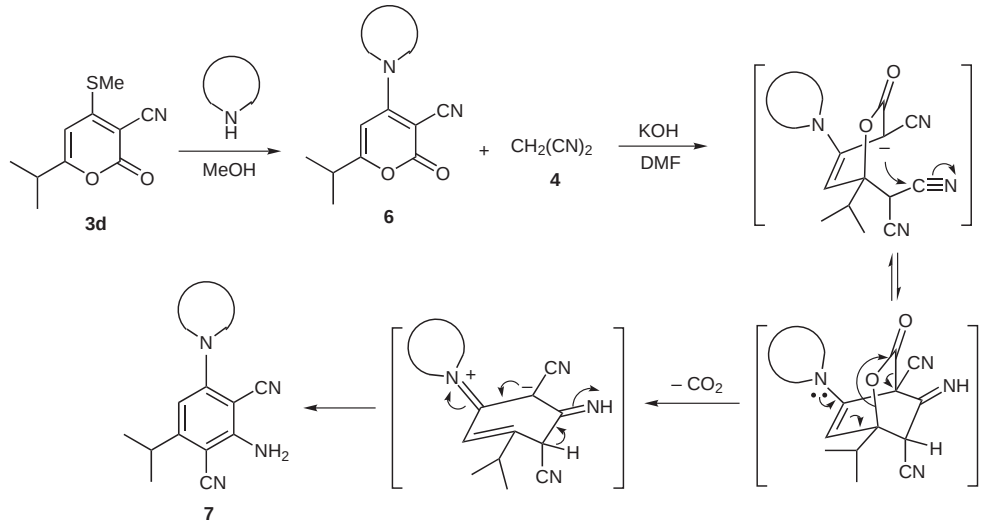
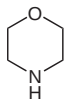
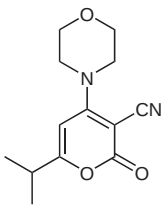
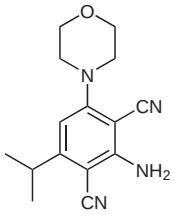
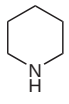
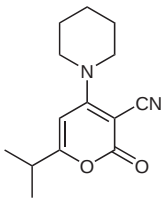
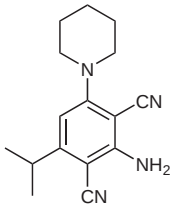
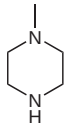
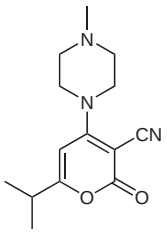
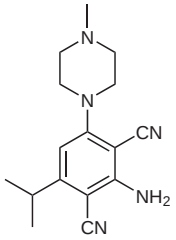
				3	**5**
a				28	89
b				36	87
c				35	90
d				52	89
e				48	91

2*H*-pyran-2-one intermediate **3**. The 2*H*-pyran-2-one intermediate is attacked by a malononitrile anion at C-6 position followed by Thorpe cyclization involving one of the nitrile functionalities of malononitrile and C-3 of the pyranone ring to form a bicyclic intermediate and further by decarboxylation to furnish the functionalized benzenes **5a**–**e** in high yields. The reaction was further exploited for the synthesis of 2-amino-4-isopropyl-6-*sec*-amino-isophthalonitriles **7a**–**c**, which are also very difficult to prepare by classical approaches. To obtain the compounds **7a**–**c**, the methylsulfanyl group of **3d** was replaced by different secondary amines. The compound 6-isopropyl-2*H*-pyran-2-one **6** was prepared in high yield by refluxing a solution of lactone **3d** with an equivalent of secondary amine in methanol for 6–8 hours (Table 2).

2-Amino-4-isopropyl-6-*sec*-amino-isophthalonitriles **7a**–**c**, were synthesized in excellent yields by stirring a mixture of 2*H*-pyran-2-ones **6a**–**c** with malononitrile (**4**) in the presence of a base. All the compounds were characterized by spectroscopic analyses.[28,29]

Table 2 Preparation of Compounds **6** and **7** from Lactone **3d**



Entry		**6**	**7**	Yield (%)	
				6	**7**
a				74	86
b				72	92
c				78	89

In summary, we have developed a new methodology for the synthesis of highly functionalized benzenes through carbanion-induced ring transformation of functionalized 2*H*-pyran-2-ones in excellent yields. This is an important methodology that offers the flexibility of introducing the electron-donor or electron-acceptor groups in the molecular architecture of benzene scaffolds. Our approach is highly simple, economical and does not require any specialized reagents or catalysts.

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(28) **General Procedure for the Synthesis of 5 and 7**: A mixture of 5-alkyl-/5,6-dialkyl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones **3** or 6-isopropyl-4-*sec*-amino-2*H*-pyran-2-ones **6** (1 mmol), malononitrile (1.2 mmol) and powdered KOH (1.2 mmol) in anhyd DMF (5 mL) was stirred at r.t. for 8–12 h. After completion of the reaction, 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 neutral alumina column using $CHCl_3$–hexane (1:9) as eluent. **5a**: yield: 89%; white solid; mp 236–238 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, Me), 2.54 (s, 3 H, SMe), 5.10 (br s, 2 H, NH_2), 6.42 (s, 1 H, ArH). ^{13}C NMR (50.0 MHz, $CDCl_3$ + DMSO): δ = 19.95, 26.68, 96.73, 98.40, 118.95, 119.83, 120.87, 152.67, 155.72, 158.00. IR (KBr): 2213 (CN), 3353, 3442 (NH_2) cm^{-1}. MS (FAB): *m*/*z* = 204 [M^+ + 1]. HRMS: *m*/*z* calcd for $C_{10}H_9N_3S$: 203.0532; found: 203.0517. **7a**: yield: 86%; white solid; mp 190–192 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.8 Hz, 6 H, 2 × Me), 3.15–3.37 (m, 5 H, CH, 2 × CH_2),

3.83–3.91 (m, 4 H, 2 × CH_2), 5.10 (br s, 2 H, NH_2), 6.17 (s, 1 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.38, 32.24, 49.76, 65.40, 85.02, 87.90, 102.70, 114.73, 115.00, 152.77, 157.62, 157.92. IR (KBr): 2210 (CN), 3353 (NH), 3412 (NH) cm^{-1}. MS (ESI): *m*/*z* = 271 [M^+ + 1]. HRMS: *m*/*z* calcd for $C_{15}H_{18}N_4O$: 270.1481; found: 270.1483.

(29) **General Procedure for the Synthesis of 6**: A mixture of compound **3d** (1.0 mmol) and secondary amine (1.2 mmol) was refluxed in MeOH (20 mL) for 6–8 h. After completion of the reaction, MeOH was evaporated under vacuum, and the reaction mixture was washed with ice-cooled H_2O. The crude was purified on a silica gel column using $CHCl_3$ as eluent. **6a**: yield 74%; white solid; mp 162–164 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.8 Hz, 6 H, 2 × Me), 2.00–2.10 (m, 4 H, 2 × CH_2), 2.62–2.73 (m, 1 H, CH), 3.54–3.62 (m, 2 H, CH_2), 4.02–4.10 (m, 2 H, CH_2), 5.71 (s, 1 H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.36, 34.00, 49.89, 66.99, 73.24, 94.52, 117.63, 161.92, 163.11, 172.59. IR (KBr): 1704 (CO), 2207 (CN) cm^{-1}. MS (ESI): *m*/*z* = 249 [M^+ + 1].