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Synthesis of ferrocenylarenes and heteroarenes through nucleophile induced ring transformation of 2*H*-pyran-2-ones☆

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Abstract—The synthesis of various ferrocenylarenes (**3**, **5a**, **6**) and heteroarenes (**5b**, **c**, **7**) from 6-ferrocenyl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile **1** through nucleophile induced ring transformation reactions has been delineated.

The significance of ferrocenyl compounds has been greatly realized in the synthesis of organomaterials[1] of unusual solid state properties by virtue of their electron donating nature and fixed intramolecular spacing. The ability of ferrocenyl derivatives to form charge transfer complexes and radical ion salts, make them highly suitable components of molecular wires,[2] anion sensors[3] and organic ferromagnets.[4] Recently, ferrocenyl derivatives were reported to display antimalarial, [5] antitumour[6] and DNA cleaving[7] activities. The biodynamic properties of this class of compounds inspired us to develop an easy access to the synthesis of ferrocenylarenes and heteroarenes.

Cyclotrimerization of alkynes in the presence of transition metal catalysts is one of the general approaches for the construction of arenes[8] either in a stepwise or concerted manner. The highly functionalized arenes are conveniently obtained from the reaction of alkynes with zirconium cyclopentadiene[9] using CuCl or $NiCl_2(PPh_3)_2$ as catalyst.[10,11] This methodology has been extensively used for the preparation of benzoheterocycles[12] and various terphenyls.[13–15] Recently, organometallic alkynes, especially ferrocenylalkynes have been used for the synthesis of ferrocenylarenes by reaction with zirconium cyclopentadiene.[15] The size of the substituent linked to the alkyne influences the rate of cyclization and yield of the reaction product. Thus it was pertinent to develop a new methodology, which could overcome the shortcomings of the earlier procedures and also provide an option for varying the substituent on the aryl ring.

Here, we report an elegant, novel route for the synthesis of various ferrocenylarenes and heteroarenes. Our approach is based on the ring transformation of 6-ferrocenyl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile **1** by either aliphatic or alicyclic or heterocyclic ketones. Carbanion nucleophiles generated from compounds containing a reactive methylene group such as malononitrile and ethyl acetoacetate have also been used for ring transformation reactions to obtain ferrocenylarenes **6** and heteroarenes **7**. Our methodology provides a general route for creating molecular diversity by selecting the reactants as per the requirement of the substituents on the aryl ring. The ring transformation reaction of 2*H*-pyran-2-ones is influenced by the presence of an electron withdrawing substituent at position 3, which facilitates the reaction by activating the pyran ring to nucleophilic attack. Thus, reaction of 6-ferrocenyl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile **1** with acetone and cyclopropyl methyl ketone in the presence of powdered KOH in DMF separately provided 4-ferrocenyl-2-methyl/cyclopropyl-6-methylsulfanylbenzonitriles **3a**,**b** while under similar reaction conditions, ethyl methyl ketone led to *o*-xylene derivative **3d** due to the formation of a carbanion at the CH_2 of the ethyl group of the ketone. Attempts to synthesize 5,5″-diferrocenyl-3,3″-bismethylsulfanyl-[1,1′,4′,1″]terphenyl-2,2″-dicarbonitrile through ring transformation of **1** using

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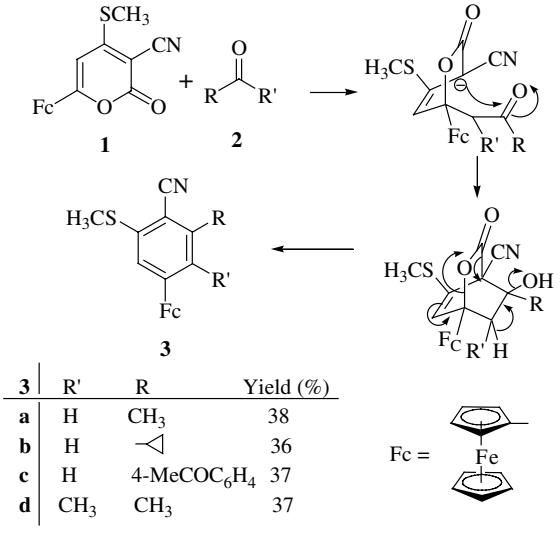
1,4-diacetylbenzene failed and in lieu only the monoferrocenyl derivative, 4-acetyl-5-ferrocenyl-3-methylsulfanyl-biphenyl-2-carbonitrile **3c** was isolated.

This reaction was further explored to assess its synthetic potential by using cyclic ketones such as cyclohexanone and *N*-substituted-4-piperidones **4** as a source of carbanion for the ring transformation reactions. Thus, reaction of **1** with cyclohexanone **4a** under similar reaction conditions to those described above gave 4-ferrocenyl-2-methylsulfanyl-5,6,7,8-tetrahydronaphthalene-1-carbonitrile **5a** while *N*-substituted-4-piperidones **4b**,**c** afforded 2-alkyl-8-ferrocenyl-6-methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline-5-carbonitriles **5b**,**c** in one step.

Reaction of **1** with reactive methylene compounds such as malonodinitrile and ethyl acetoacetate did not proceed analogously. Thus, a reaction of 1 with malonodinitrile led to 2-amino-4-ferrocenyl-6-methylsulfanyl-benzo-1,3-dinitrile **6** in 42% yield while reaction with ethyl acetoacetate gave the fused bicyclic oxygen heterocycle, pyrano[3,4-*c*]pyranone **7** in 55% yield.

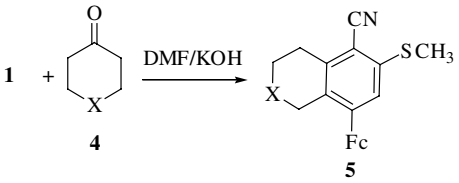
The position 6 in 2*H*-pyran-2-one **1** is highly susceptible to nucleophilic attack due to extended conjugation and the presence of an electron withdrawing substituent at position 3 of the pyran ring. Possibly, the ring transformation reaction is initiated by attack of the carbanion generated in situ from ketones at position 6 of the pyran ring with ring-opening followed by decarboxylation and recyclization to provide ferrocenylarenes and heteroarenes **3** and **5** as depicted in Schemes 1 and 2. As an exception, the carbanion generated from ethyl acetoacetate attacks at position 4 of the pyran ring followed by cyclization involving the nitrile group at position 3 and the enolic functionality of ethyl acetoacetate to yield pyrano[3,4-*c*]pyranone **7** (Scheme 3).

All the synthesized compounds were characterized[16] by spectroscopic and elemental analyses.



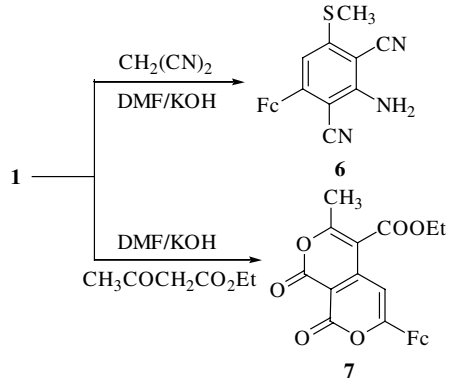
3	R'	R	Yield (%)
a	H	CH_3	38
b	H		36
c	H	4-$MeCOC_6H_4$	37
d	CH_3	CH_3	37

Scheme 1.



5	X	Yield (%)
a	CH_2	42
b	$NCO_2C_2H_5$	39
c	NC_2H_5	40

Scheme 2.



Scheme 3.

Our methodology for the synthesis of ferrocenylarenes and heteroarenes is very simple, economical and moreover has the option for varying the substituents on the aryl ring and does not require the use of a catalyst.

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16. *Typical procedure for* **3a**: A mixture of **1** (1 mmol) and dry acetone (1 mmol) was stirred in a suspension of KOH (1.5 mmol) and dry DMF (15 mL) for 24 h at room temperature. The reaction mixture was poured onto ice-water and neutralized with 10% HCl. The separated solid was filtered, washed with water and dried. The crude product was purified by silica gel column chromatography using hexane–ethyl acetate (99:1) as eluent.
Compound **3a**: mp 154–156 °C; IR (KBr) ν 2212 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.53 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 4.06 (s, 5H, ferrocenyl), 4.41 (bs, 2H, ferrocenyl), 4.66 (bs, 2H, ferrocenyl), 7.15 (s, 1H, ArH), 7.20 (s, 1H, ArH); MS (FAB) 348 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{17}FeNS$ C, 65.72; H, 4.93; N, 4.03%. Found: C, 65.95; H, 5.10; N, 4.32%.
Compound **3b**: mp 132–134 °C; IR (KBr) ν 2211 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 0.79–0.88 (m, 4H, $2CH_2$), 2.20–2.40 (m, 1H, CH), 2.59 (s, 3H, SCH_3), 4.05 (s, 5H, ferrocenyl), 4.39–4.41 (m, 2H, ferrocenyl), 4.63–4.64 (m, 2H, ferrocenyl), 6.78 (s, 1H, ArH), 7.17 (s, 1H, ArH); MS (FAB) 374 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{19}FeNS$ C, 67.57; H, 5.13; N, 3.75. Found: C, 67.80; H, 5.33; N, 3.43.
Compound **3c**: mp 150–152 °C; IR (KBr) ν 2211 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.65 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 4.08 (s, 5H, ferrocenyl), 4.45–4.47 (m, 2H, ferrocenyl), 4.69–4.71 (m, 2H, ferrocenyl), 7.29 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.67 (d, J = 8.29 Hz, 2H, ArH), 8.10 (d, J = 8.34 Hz, 2H, ArH); MS (FAB) 452 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{21}FeNOS$ C, 69.19; H, 4.69; N, 3.10%. Found: C, 69.29; H, 4.48; N, 3.32%.
Compound **3d**: mp 144–146 °C; IR (KBr) ν 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.62 (s, 3H, SCH_3), 4.15 (s, 5H, ferrocenyl), 4.37 (bs, 2H, ferrocenyl), 4.45 (bs, 2H, ferrocenyl), 7.63 (s, 1H, ArH). MS (FAB) 362 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{19}FeNS$ C, 66.49; H, 5.30; N, 3.88%. Found: C, 66.23; H, 5.13; N, 4.05%.
Compound **5a**: mp 190–192 °C; IR (KBr) ν 2206 cm^{-1} (CN), ^1H NMR (200 MHz, $CDCl_3$) δ 1.66–1.86(m, 4H, 2 CH_2), 2.62 (s, 3H, SCH_3), 2.68 (t, J = 6.10 Hz, 2H, CH_2), 2.97 (t, J = 6.41 Hz, 2H, CH_2), 4.15 (s, 5H, ferrocenyl), 4.35–4.37 (m, 2H, ferrocenyl), 4.45–4.47 (m, 2H, ferrocenyl), 7.62 (s, 1H, ArH); MS (FAB) 388 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{21}FeNS$ C, 68.22; H, 5.47; N, 3.62%. Found: C, 68.54; H, 5.78; N, 3.51%.
Compound **5b**: oil; IR (KBr) ν 2217 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.08 Hz, 3H, CH_3), 2.62 (s, 3H, SCH_3), 3.10 (t, J = 6.05 Hz, 2H, CH_2), 3.71 (t, J = 6.10 Hz, 2H, CH_2), 4.10–4.16 (m, 2H, OCH_2), 4.19 (s, 5H, ferrocenyl), 4.42–4.43 (m, 2H, ferrocenyl), 4.49–4.51 (m, 2H, ferrocenyl), 4.69 (s, 2H, CH_2), 7.56 (s, 1H, ArH); MS (FAB) 461 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{24}FeN_2O_2S$ C, 62.62; H, 5.25; N, 6.09%. Found: C, 62.84; H, 5.53; N, 6.25%.
Compound **5c**: mp 118–120 °C; IR (KBr) ν 2214 cm^{-1} (CN), ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (t, J = 7.24 Hz, 3H, CH_3), 2.57–2.61 (m, 2H, CH_2), 2.62 (s, 3H, SCH_3), 2.76–2.79 (m, 2H, CH_2), 3.09–3.11 (m, 2H, CH_2), 3.58 (s, 2H, CH_2), 4.16 (s, 5H, ferrocenyl), 4.37–4.38 (m, 2H, ferrocenyl), 4.44–4.46 (m, 2H, ferrocenyl), 7.61 (s, 1H, ArH); MS (FAB) 417 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{24}FeN_2S$ C, 66.35; H, 5.81; N, 6.73%. Found: C, 66.76; H, 5.60; N, 6.94%.
Compound **6**: mp 228–230 °C; IR (KBr) ν 2210 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.59 (s, 3H, SCH_3), 4.19 (s, 5H, ferrocenyl), 4.49–4.52 (m, 2H, ferrocenyl), 4.90–4.91 (m, 2H, ferrocenyl), 5.17 (bs, 2H, NH_2), 6.69 (s, 1H, ArH); MS (FAB) 374 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{15}FeN_3S$ C, 61.14; H, 4.05; N, 11.26%. Found: C, 61.45; H, 4.28; N, 10.97%.
Compound **7**: mp 260–262 °C; IR (KBr) ν 1712 cm^{-1} (CO), 1789 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.46 (t, J = 7.13 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.23 (s, 5H, ferrocenyl), 4.46 (q, J = 7.14 Hz, 2H, CH_2), 4.64–4.66 (m,2H, ferrocenyl), 4.89–4.92 (m, 2H, ferrocenyl), 6.75 (s, 1H, CH); MS (FAB) 435 ($M^+ + 1$); Anal. Calcd for $C_{22}H_{18}FeO_6$ C, 60.85; H, 4.18%. Found: C, 60.63; H, 4.31%.