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Facile Synthesis of m-Terphenyls by Ring Transformation of 2H-Pyran-2-ones

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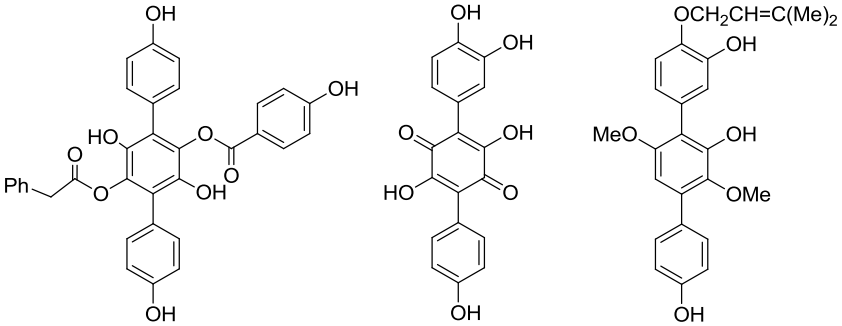
ABSTRACT

An alternative approach for the synthesis of meta-terphenyls 3a-g functionalized with electron-withdrawing or -donating groups is described and illustrated by carbanion-induced ring transformation of 6-aryl-2H-pyran-2-ones 1a-g with propiophenone 2 in excellent yields.

Keywords: 2*H*-Pyran-2one, Ring transformation reaction, Nucleophile, Terphenyls

INTRODUCTION

The chemistry of terphenyls has been developed as an important research area in organic chemistry. Terphenyls bearing electron donating and accepting functionalities are the key components several mushrooms belonging to the Thelephoraceae family [1-4]. Theleforin A 1 was isolated from fruiting bodies of the mushroom *Thelephora vialis* and exhibits antioxidant activity [5]. Furthermore, atromentin 2 was isolated from methanolic extract of fruiting bodies of the mushroom *Thelephora aurantiotincta* [6]. Terprenin 3 was obtained from the fermentation broth of *Aspergillus candidus* RF-5672 [7-9] and identified as potent immunoglobulin E antibody suppressant [10,11]. There are several other terphenyl-cored naturally occurring compounds reported in past decades and known for diverse biological properties (Figure 1) [6-13].



1: Thelephorin A **2: Atromentin** **3: Terprenin**

Figure 1: Naturally occurring compounds 1-3 having terphenyl architecture

Various synthetic terphenyls have been proved their importance in medicinal and pharmaceutical chemistry. Few terphenyl derivatives have been designed as selective inhibitors for dihydroortate dehydrogenase [14] and cyclooxygenase enzymes [15]. In addition, few synthetic terphenyls have been developed as potent antidiabetic agents [16-18].

MATERIALS AND METHODS

Melting points were obtained in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded on a AV-400 Bruker using the solvents indicated with 400 and 100 MHz, respectively, also a DRX-500 Bruker was used in the some cases for ^{1}H (500 MHz) and

^{13}C (125 MHz). Mass spectra (*m*/*z*) were recorded under the conditions of electron impact (EI) and electrospray (ES) and chemical ionization (CI). All reactions were monitored by thin-layer chromatography that was performed on pre-coated sheets of silica gel 60, and column chromatography was performed with silica gel 60 (Avra synthesis, 100–200 mesh). Eluting solvents are indicated in the text. Dry THF was used from a solvent purification system while acetonitrile of HPLC grade was used and dried with molecular sieves (4 Å). All other purchased chemicals were used without further purification.

EXPERIMENTAL SECTION

General procedure for the synthesis of compounds 3a-g

A mixture of 6-aryl-2*H*-pyran-2-one (1) (1.0 mmol), propiophenone (2) (1.2 mmol) and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 10-15 h. The course of reaction was monitored with TLC. After the completion of 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 EtOAc-hexane (1:9) as eluent. The isolated compounds were characterized as m-terphenyls 3 by their spectroscopic analysis.

2'-Methyl-5'-(piperidin-1-yl)-[1,1':3',1''-terphenyl]-4'-carbonitrile 3a

White solid; mp 112-114°C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 1.58-1.68 (m, 2H, CH_2), 1.75-1.90 (m, 4H, $2CH_2$), 3.00-3.20 (m, 4H, $2CH_2$), 6.88 (s, 1H, ArH), 6.91-7.02 (m, 4H, ArH), 7.06-7.23 (m, 6H, ArH); IR (KBr) 2210 cm^{-1} (CN); MS (ESI) 353 (M^++1).

4-Fluoro-2'-methyl-5'-(piperidin-1-yl)-[1,1':3',1''-terphenyl]-4'-carbonitrile 3b

White solid; mp 132-134°C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H, Me), 1.60-1.69 (m, 2H, CH_2), 1.76-1.90 (m, 4H, $2CH_2$), 3.03-3.22 (m, 4H, $2CH_2$), 6.91 (s, 1H, ArH), 6.88-7.03 (m, 4H, ArH), 7.12 (d, *J* = 8.4 Hz, 2H, ArH), 7.17-7.24 (m, 3H, ArH); $^{13}CNMR$ (100 MHz, $CDCl_3$) 25.3, 26.8, 31.9, 105.4, 117.8, 118.9, 127.6, 128.4, 128.6, 130.9, 132.5, 133.7, 134.9, 139.5, 140.3, 145.6, 152.6, 158.5; IR (KBr) 2213 cm^{-1} (CN); MS (ESI) 471 (M^++1).

4-Chloro-2'-methyl-5'-(piperidin-1-yl)-[1,1':3',1''-terphenyl]-4'-carbonitrile 3c

White solid; mp 121-123ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 1.56-1.69 (m, 2H, CH_2), 1.73-1.91 (m, 4H, $2CH_2$), 3.01-3.22 (m, 4H, $2CH_2$), 6.85 (s, 1H, ArH), 6.83-7.02 (m, 4H, ArH), 7.09 (d, *J* = 8.4 Hz, 2H, ArH), 7.13-7.22 (m, 3H, ArH); $^{13}CNMR$ (100 MHz, $CDCl_3$) 25.5, 26.7, 31.3, 105.7, 117.8, 118.8, 127.5, 128.3, 128.4, 130.6, 132.4, 133.6, 134.8, 139.5, 140.3, 145.6, 152.3, 158.3; IR (KBr) 2215 cm^{-1} (CN); MS (ESI) 387 (M^++1), 387 (M^++3).

4-Bromo-2'-methyl-5'-(piperidin-1-yl)-[1,1':3',1''-terphenyl]-4'-carbonitrile 3d

White solid; mp 140-142ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 1.58-1.70 (m, 2H, CH_2), 1.70-1.92 (m, 4H, $2CH_2$), 2.99-3.1 (m, 4H, $2CH_2$), 6.84 (s, 1H, ArH), 6.88-7.03 (m, 4H, ArH), 7.08 (d, *J* = 8.4 Hz, 2H, ArH), 7.12-7.24 (m, 3H, ArH); $^{13}CNMR$ (100 MHz, $CDCl_3$) 25.8, 26.3, 31.7, 106.1, 117.6, 118.3, 127.4, 128.6, 128.7, 130.9, 132.8, 133.3, 134.4, 139.3, 140.6, 145.2, 152.6, 158.8; IR (KBr) 2215 cm^{-1} (CN); MS (ESI) 431 (M^++1), 387 (M^++3).

2',4-Dimethyl-5'-(piperidin-1-yl)-[1,1':3',1''-terphenyl]-4'-carbonitrile 3e

White solid; mp 146-148ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H, Me), 2.36 (s, 3H, Me), 1.59-1.66 (m, 2H, CH_2), 1.72-1.87 (m, 4H, $2CH_2$), 3.01-3.20 (m, 4H, $2CH_2$), 6.72 (d, *J* = 8.6 Hz, 2H, ArH), 6.82-7.03 (m, 5H, ArH), 7.14-7.24 (m, 3H, ArH); IR (KBr) 2217 cm^{-1} (CN); MS (ESI) 367 (M^++1).

4-Methoxy-2'-methyl-5'-(piperidin-1-yl)-[1,1':3',1''-terphenyl]-4'-carbonitrile 3f

White solid; mp 146-148ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 1.58-1.67 (m, 2H, CH_2), 1.75-1.89 (m, 4H, $2CH_2$), 3.00-3.20 (m, 4H, $2CH_2$), 3.73 (s, 3H, OMe), 6.67 (d, *J* = 8.6 Hz, 2H, ArH), 6.84-7.01 (m, 5H, ArH), 7.16-7.25 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 24.9, 26.7, 32.2, 55.4, 104.7, 116.9, 117.8, 127.2, 128.5, 129.2, 131.5, 133.5, 133.9, 134.7, 138.7, 140.1, 144.8, 152.8, 157.6; IR (KBr) 2214 cm^{-1} (CN); MS (ESI) 383 (M^++1).

3-Methoxy-2'-methyl-5'-(piperidin-1-yl)-[1,1':3',1''-terphenyl]-4'-carbonitrile 3g

White solid; mp 158-160ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 1.57-1.67 (m, 2H, CH_2), 1.73-1.88 (m, 4H, $2CH_2$), 2.99-3.18 (m, 4H, $2CH_2$), 3.76 (s, 3H, OMe), 6.66-6.78 (m, 1H, ArH), 6.83-7.03 (m, 4H, ArH), 7.16-7.25 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 24.6, 26.5, 32.4, 55.6, 104.5, 116.7, 117.6, 127.2, 128.4, 128.9, 131.6, 133.4, 133.6, 134.5, 138.6, 140.3, 144.6, 152.5, 157.4; IR (KBr) 2214 cm^{-1} (CN); MS (ESI) 383 (M^++1).

RESULT AND DISCUSSION

Synthesis of *m*-terphenyl has been achieved by using both classical and non-classical approaches. In classical approaches, *m*-terpheyls have been synthesized by transition metal-catalyzed cross coupling reactions of electrophilic and nucleophilic reaction partners. In 2015, Larrosa et al. developed Pd-catalyzed synthesis of *m*-terphenyl by cross-coupling reaction of 1,3-dichloroarene as electrophile and aryl magnesium bromide as nucleophile [19]. Furthermore, Wang et al. achieved the synthesis of *m*-terphenyls by Pd-catalyzed denitrogenative Hiyama coupling of arylhydrazine with triethoxy(phenyl)silane [20]. Recently, Sandford and et al.

developed a direct approach for the synthesis of polyfluorinated *m*-terphenyls by Pd-catalyzed Suzuki-Miyaura coupling of phenyl boronic acids with polyfluorinated nitro benzene [21]. There was a solitary approach in which nickel catalyst was used to achieve the synthesis of *m*-terphenyls [22]. In addition, there are some non-classical approaches used for the synthesis of *m*-terphenyls including triphyrin-catalyzed reaction of aryliodine with benzene [23], organocatalytic reaction of iodoarene with benzene [24], base-promoted homolytic aromatic substitution 3-chloroiodobenzene with benzene [25] and base-promoted benzannulation reaction 3-formylchromones with 1,3-diphenyl-2-propanone [26]. In addition, ring transformation of 2*H*-pyran-2one is another non-classical approach that is successfully used for thesis of *o*-, *m*- and *p*-terphenyls [27,28].

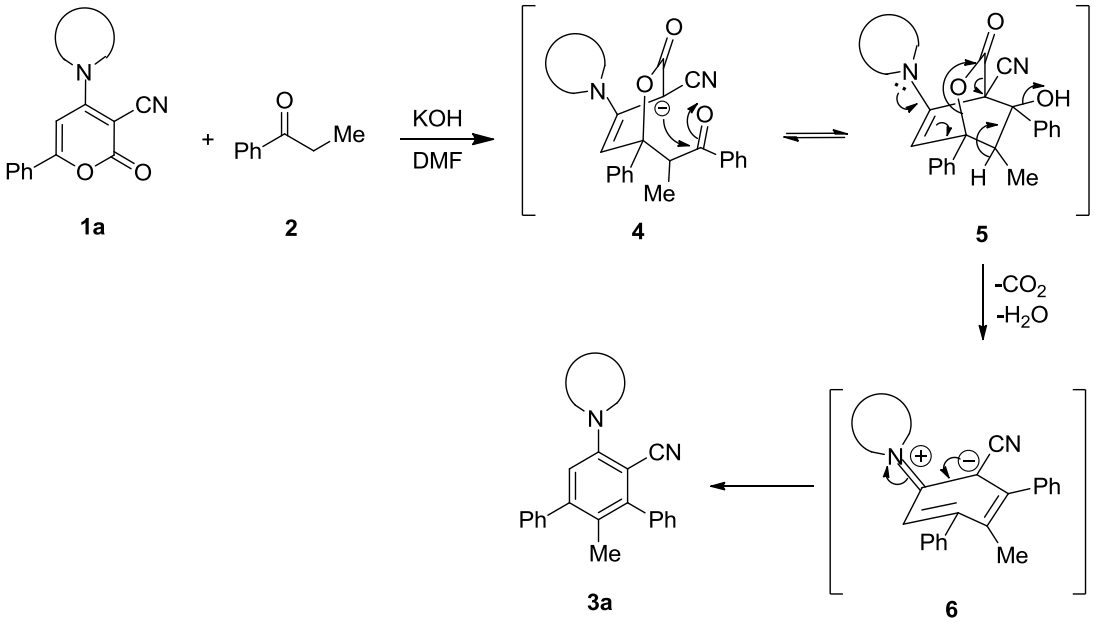
The wide-ranging applications and high demand of terphenyls and paucity of non-metal catalyzed synthetic methodologies prompted us to develop a simple, general and efficient route for the synthesis of *m*-terphenyls. Herein, we report synthesis of functionalized *meta*-terphenyls through reaction of 2*H*-pyran-2-ones 1 with propiophenone 2 in high yields at room temperature without using an organometallic reagent or a catalyst. The advantage of the procedure lies in the creation of a central benzene ring under mild reaction conditions from 2*H*-pyran-2-one at room temperature [29-35].

Our approach to prepare functionalized *m*-terphenyls 3a-g is based on the ring transformation of 6-aryl-2-oxo-4-(piperidin-1-yl)-2*H*-pyran-3-carbonitriles 1a-g using propiophenone 2 as a carbanion source. The 2*H*-pyran-2-ones 1a–g precursors were synthesized by the reaction of ethyl 2-carbomethoxy-3,3-di(methylsulfanyl)-acrylate with substituted acetophenones under alkaline conditions followed by the reaction with cyclic amines [19]. Lactones, 1a–g has three electrophilic centres: C2, C4 and C6 in which the latter position is highly reactive towards nucleophiles due to the extended conjugation and the presence of the electron-withdrawing substitutent at position 3 of the pyran ring. In a typical process, stirring an equimolar mixture of 2*H*-pyran-2-ones 1a-g, propiophenone 2 and powdered KOH in DMF for 10-15 h at room temperature afforded functionalized *m*-terphenyls 3a-g in 75-89% yields (Table 1). Various electron-withdrawing and donating functionalities were successfully tolerated in the reaction. It was also observed that course of reaction was almost same with both electron-withdrawing and donating substituents on aromatic ring at C6 position of 2*H*-pyran-2one 3. All the synthesized compounds were characterized by the spectroscopic analysis.

The possible mechanism of ring transformation reaction is depicted in Scheme 1. The transformation of 6-aryl-2*H*-pyran-2-ones 1 into *m*-terphenyls is possibly initiated by attack of the carbanion generated from 2 at position C6 of lactone 1a-g, followed by intramolecular cyclization involving the carbonyl functionality of 2 and C3 of the pyranone ring and elimination of carbon dioxide, followed by protonation and dehydration to yield 3a-g in good yields.

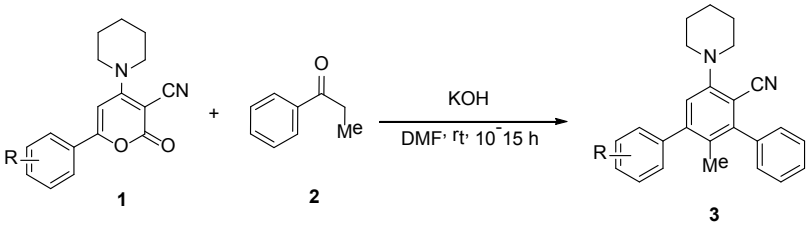
CONCLUSION

In summary, we have developed a new synthetic methodology for preparing functionalized *meta*-terphenyls through the carbanion-induced ring transformation of 2*H*-pyran-2-ones, in good yields. The methodology is very simple, economical and does not require any specialized organometallic reagents or catalysts. This methodology is a potentially useful alternative to conventional metal-catalyzed cross-coupling reactions.



Scheme 1: Ring transformation reaction

Table 1: Synthesis of *m*-terphenyls 3a-g via ring transformation of 6-aryl-2-oxo-4-(piperidin-1-yl)-2*H*-pyran-3-carbonitriles 1a-g with propiophenone 2



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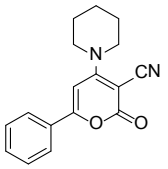
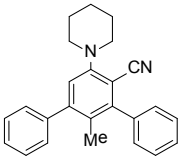
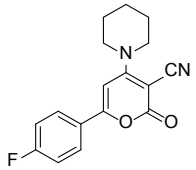
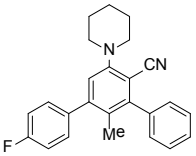
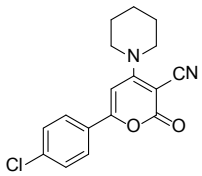
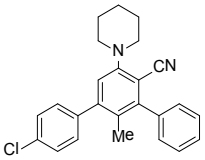
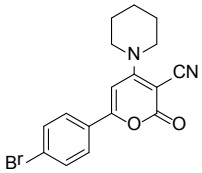
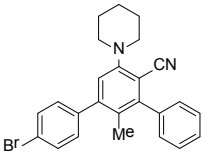
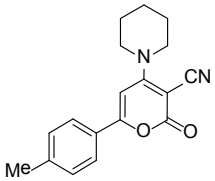
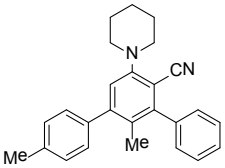
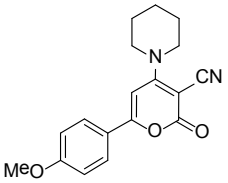
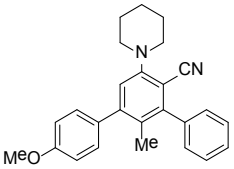
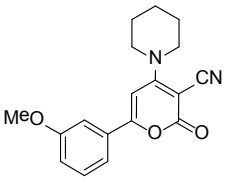
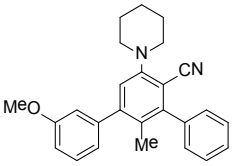
a			12	81
b			10	85
c			10	83
d			11	89
e			13	75
f			15	86
g			15	83

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