Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 10971–10978

Regioselective synthesis of 2-amino-isophthalonitriles through a ring transformation strategy☆

Fateh V. Singh,[a] Vijay Kumar,[a] Brijesh Kumar[b] and Atul Goel[a,*]

[a]*Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226001, India*
[b]*Division of Sophisticated Analytical Instrument Facility, Central Drug Research Institute, Lucknow 226001, India*

Received 15 June 2007; revised 28 July 2007; accepted 16 August 2007
Available online 22 August 2007

Abstract—An expeditious synthesis of several 2-amino-isophthalonitriles and their biaryl compounds is described and illustrated by carbanion-induced ring transformation of functionalized 2*H*-pyran-2-ones with malononitrile in excellent yields. The strength of the reaction lies in the creation of an aromatic ring at room temperature from six-membered lactones under mild reaction conditions. This approach is an alternative to Diels–Alder reactions of 2*H*-pyran-2-ones with dienophiles, which require forcing thermal conditions to obtain benzene derivatives.

1. Introduction

Benzene scaffolds functionalized with an amino functionality flanked between two nitrile substituents not only possess important biological properties[1–3] but are also useful precursors for the synthesis of quinazolines[4] and fluorenones.[5] The synthesis of highly functionalized benzenes in a regioselective manner is a challenging task.[6] Direct functional group attachment onto the benzene scaffolds by electrophilic or nucleophilic substitution reactions[7] such as directed-*ortho*-metalation reactions,[8] metal-catalyzed coupling reactions,[9] and metalation–functionalization reactions[10] offers a versatile approach to the synthesis of di- and trisubstituted benzene analogues. However, applications of these approaches to the synthesis of hexasubstituted benzene systems suffer from low positional selectivity of electron donating or withdrawing groups and/or orienting effects of the substituents.

The construction of benzene skeletons from acyclic precursors includes benzannulation reactions such as Danheiser alkyne–cyclobutenone cyclization,[11] [3+2+1]-Dötz reaction of Fisher carbene complexes,[12] [4+2]-cycloaddition of metalacyclopentadienes and alkynes,[13] [4+2]-Yamamoto benzannulation of *o*-alkynyl benzaldehyde and alkyne,[14] [2+2+2]- and [4+2]-cycloaddition reactions in the presence of transition metal catalyst,[15] via [4+2]-annulation of Baylis–Hillman adducts,[16] and [3+3]-cyclocondensation between bielectrophiles and binucleophiles.[17] Although these benzannulation approaches afforded wide variety of aromatic compounds utilization of these protocols for the preparation of functionally congested benzenes such as substituted isophthalonitriles places constraints on the choice of reagents or conditions. Isophthalonitriles have been either synthesized by the reaction of α,β-unsaturated carbonyl compounds with malononitrile[4a,18] or by the reaction of α-methylene ketones and enaminoketones with malononitrile[19] separately, but these procedures require either access of starting material and high temperature or produce low yields of the desired isophthalonitriles. 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 a benzene scaffold.

Herein, we report an efficient and convenient procedure for the synthesis of highly functionalized isophthalonitriles and their biaryl compounds through carbanion-induced ring transformation of 2*H*-pyran-2-ones using malononitrile as a source of the carbanion. The advantage of the procedure lies in the creation of a benzene ring generated through lactonization at room temperature without using an organometallic reagent or a catalyst, or harsh reaction conditions.

2. Results and discussion

2*H*-Pyran-2-one derivatives are of interest due to diverse synthetic applications as a diene component in Diels–Alder reactions.[20] During our recent studies on 2*H*-pyran-2-ones, we developed new protocols for the synthesis of arenes,[21]

☆ CDRI Communication No. 7253.
Keywords: Isophthalonitrile; Benzene; Biaryl; Lactone; 2*H*-Pyran-2-one; Malononitrile.
* Corresponding author. Fax: +91 522 2623405; e-mail: agoel13@yahoo.com

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.08.056

pyridines,[22] pyridones,[23] and polyarylbenzenes[24] through nucleophile-induced ring transformation reactions.

The *2H*-pyran-2-one ring system **3** possesses three electrophilic centers; C-2, C-4 and C-6 in which C-6 is highly prone to nucleophilic attack due to the extended conjugation and the presence of the electron withdrawing substitutent at position 3 of the pyranone ring.

2.1. Synthesis of 5,6-dialkyl-2-amino-4-isophthalonitriles

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[25] **3a–e** used as parent precursors have been prepared by the reaction of methyl 2-cyano-3,3-dimethylsulfanylacrylate **1** with methylene carbonyl compounds **2a–e** under alkaline conditions in high yields (Scheme 1). These 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 h at room temperature[21c] (Scheme 1). The reaction was monitored by TLC and thereafter the reaction mixture was 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. The ^{1}H NMR spectrum of compound **5a** showed two singlets at δ 2.48 ppm and 2.54 ppm due to Me and SMe groups, respectively, a broad singlet at δ 5.10 ppm for 2H due to NH_2 group and a singlet at δ 6.42 ppm for 1H due to CH of the aromatic ring. A band at 2212 cm^{-1} in the IR spectrum and molecular ion peak *m/z* at 204 confirmed the structure of compound **5a** as 2-amino-4-methyl-6-methylsulfanyl-isophthalonitrile.

The plausible reaction mechanism for the formation of **5a–e** is based on Michael–Ziegler–Thorpe-retro-Diels–Alder type reaction of **3** with active methylene compounds under mild reaction conditions as depicted in Scheme 1. The reaction is initiated by the Michael addition of an anion, generated from a molecule of ketone **2**, to the ketene-*S*,*S*-acetal **1** followed by intramolecular cyclization to form a 2*H*-pyran-2-one intermediate **3**. The 2*H*-pyran-2-one is attacked by a hard malononitrile anion at the hard electrophilic center (C-6 position), followed by Ziegler–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 benzenes **5a–e** in high yields.

The reaction was further exploited for the synthesis of 6-substituted-2-amino-4-isopropylisophthalonitriles **7a–c**, which are difficult to prepare by classical approaches. To obtain the compounds **7a–c**, the soft electrophilic carbon–sulfur bond in **3d** was replaced by soft nucleophilic secondary amines to furnish 6-isopropyl-4-secondaryamino-2*H*-pyran-2-ones (**6a–c**). The compounds **6a–c** were prepared in high yields by refluxing a solution of lactone **3d** with an equivalent of different secondary amines in methanol for 6–8 h (Scheme 1). 2-Amino-isophthalonitriles **7a–c** were synthesized in high yields by stirring a mixture of 2*H*-pyran-2-ones **6a–c** with malononitrile **4** in the presence of KOH in DMF. All the compounds were characterized by spectroscopic analysis.

2.2. Synthesis of 6-alkyl-5-aryl-2-amino-4-isophthalonitriles

In order to generalize our methodology, we focused on the preparation of functionalized biaryls, which are not only the central building motifs of a large number of natural products[26] and pharmaceuticals but also useful as versatile auxiliaries for asymmetric syntheses,[27] as chiral phases for chromatography,[28] and as important substrates for chiral liquid crystalline materials.[29]

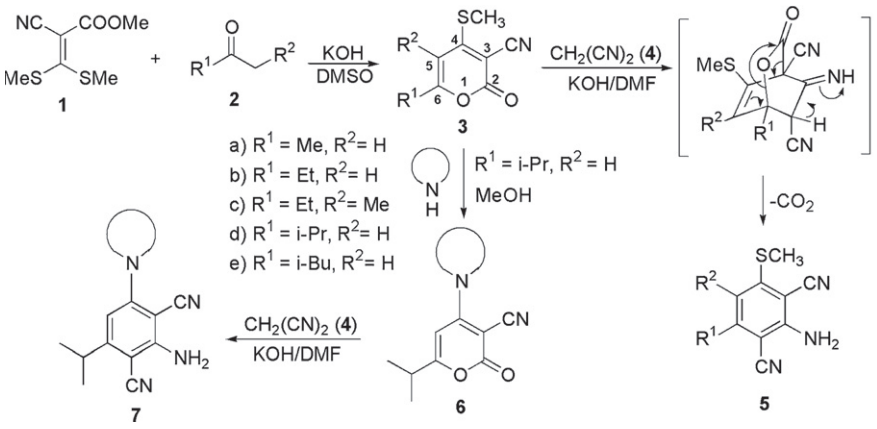
Aryl–aryl bond formation for the preparation of symmetrical and unsymmetrical biaryl compounds is one of the most useful and important tools in modern organic chemistry. The construction of the biaryl axis can be achieved either by intermolecular or intramolecular cross-coupling of two similar or dissimilar aromatic rings in the presence of transition metal catalyst.[8a,30–32] However, these metal-assisted cross-coupling reactions are associated with the requirements for expensive organometallic reagents/catalysts, high temperature reaction conditions, and undesired byproducts. Therefore, transition metal-free synthetic approaches for the synthesis of unsymmetrical biaryls are in demand. Thus, it was envisaged that 6-aryl-2*H*-pyran-2-one on reaction with malononitrile would analogously furnish biaryls at room temperature.

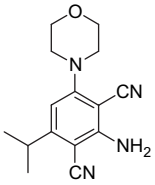
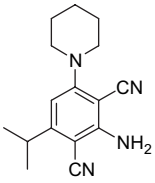
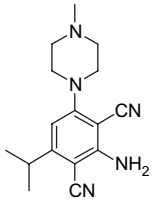
Our synthetic approach to preparing functionalized biaryls **10a–f** was based on ring transformation of 6-alkyl-5-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones **9a–f** by using malononitrile.[21d] The 6-alkyl-5-aryl-2*H*-pyran-2-ones **9a–f** used as parent precursors were prepared by the reaction of methyl 2-cyano-3,3-dimethylsulfanylacrylate[25] **1** with substituted phenyl acetones under alkaline conditions in high yields (Scheme 2). The biaryl compounds **10a–f** were synthesized by stirring an equimolar mixture of 6-alkyl-5-aryl-2*H*-pyran-2-ones **9a–f**, malononitrile, and powdered KOH in DMF for 12–15 h at room temperature (Scheme 2). The reaction was monitored by TLC and thereafter the reaction mixture was poured into ice water and neutralized with dilute HCl. The crude product thus obtained was purified on silica gel column.

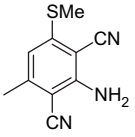
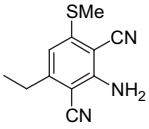
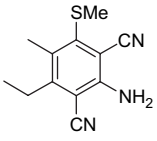
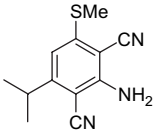
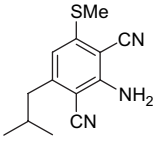
2.3. Synthesis of 5-alkyl-6-aryl-2-amino-4-isophthalonitriles

The reaction was further exploited by synthesizing precursors 6-aryl-5-methyl-2*H*-pyran-2-ones **11a–c**. An equimolar mixture of ketene dithioacetal **1** and substituted propiophenones in dry DMSO afforded 6-aryl-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles **11a–c** in 80–90% yields (Scheme 3). The 2*H*-pyran-2-ones **11a–c** were reacted with malononitrile in the presence of a base to afford 3-amino-6-methyl-5-methylsulfanyl-biphenyl-2,4-dicarbonitriles **12a–c** in high yields.[21d] The potential of the reaction lies in the conversion of the lactone ring into an aromatic ring involving the $-CH_2CN$ unit of the malononitrile **4**, in the presence of a base at room temperature.

Finally the reaction was generalized by preparing 3-amino-6-methyl-5-amin-1-yl-biphenyl-2,4-dicarbonitriles **14a–c** using 6-aryl-5-methyl-2-oxo-4-amin-1-yl-2*H*-pyran-3-carbonitriles **13a–c** as precursors. The 6-aryl-5-methyl-2-oxo-4-amin-1-yl-2*H*-pyran-3-carbonitriles **13a–c** were prepared in high yields by refluxing a solution of lactone **11** with



Structure	Reaction time (h)	Yield (%)
 **7a**	10	86
 **7b**	9	92
 **7c**	8	89

Structure	Reaction time (h)	Yield (%)
 **5a**	8	89
 **5b**	9	87
 **5c**	12	90
 **5d**	10	89
 **5e**	12	91

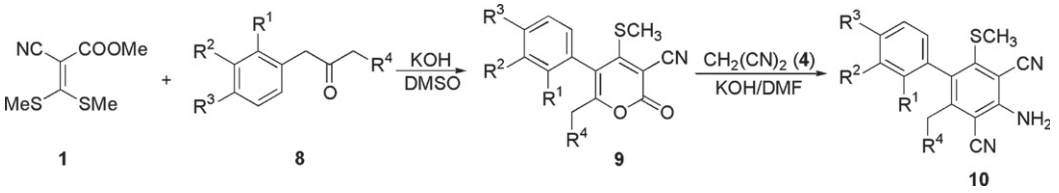
Scheme 1.

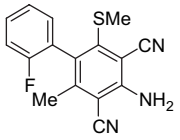
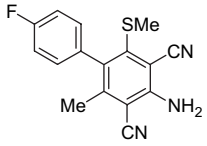
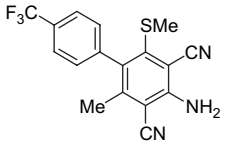
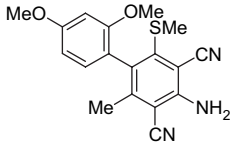
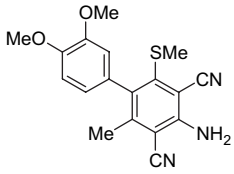
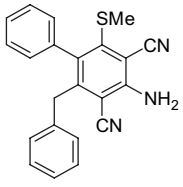
either an equivalent of 4-methylpiperidine or piperidine in methanol for 6–8 h (Scheme 3).

The synthesis of 3-amino-6-methyl-5-amin-1-yl-biphenyl-2,4-dicarbonitriles **14a–c** was achieved by stirring an equimolar mixture of 2*H*-pyran-2-ones **13a–c**, malononitrile **4**, and powdered KOH in DMF for 14–16 h at room temperature as shown in Scheme 3.

3. Conclusion

In summary, we have developed a new methodology for the synthesis of functionalized isophthalonitriles and their biaryl scaffolds in which an amino functionality is flanked in-between two nitrile substituents through carbanion-induced ring transformation of functionalized 2*H*-pyran-2-ones in high yields. This is an important methodology that offers



Entry 10	Structure	Reaction time (h)	Yield (%)
a		12	94
b		14	87
c		12	90
d		15	89
e		12	91
f		13	92

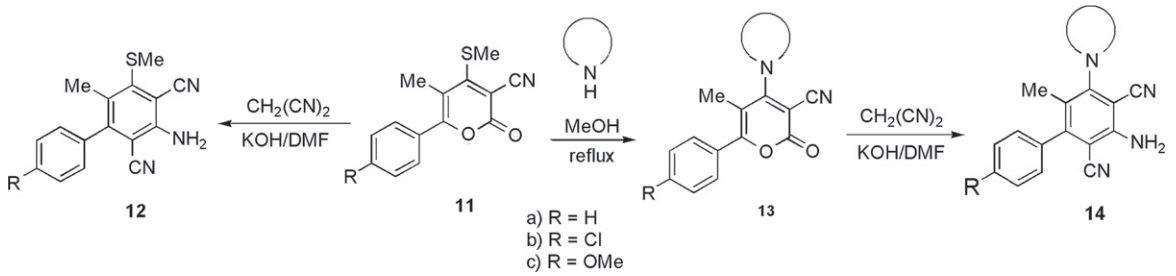
Scheme 2.

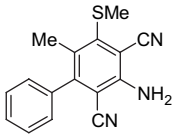
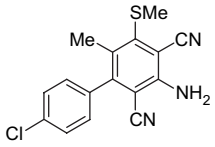
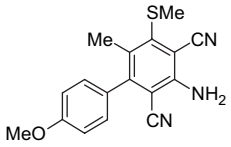
the flexibility of introducing the electron donor or acceptor groups in the molecular architecture of benzene scaffolds. Our approach is highly simple, economical and does not require any specialized organometallic reagents or catalysts.

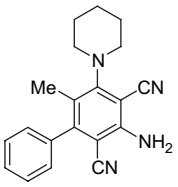
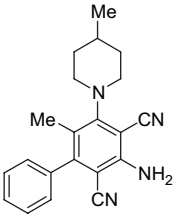
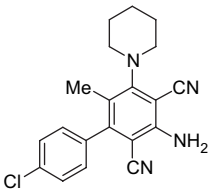
4. Experimental

4.1. General

^{1}H NMR spectra were taken on a Bruker WM-200 at 200 MHz. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million shift (δ-value) from Me_4Si (δ 0 ppm for ^{1}H) as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Coupling constants (J) are given in hertz. Infrared (IR) spectra were recorded on a Perkin–Elmer AX-1 spectrophotometer in KBr disc and are reported in wave number (cm^{-1}). Fast-atomic bombardment (FAB) spectrometer was used for mass spectra analysis. HRMS spectra were recorded on JEOL-MS route JMS-600H spectrometer. Melting points were measured with Buchi-530 melting point apparatus. All the reactions were carried out in dry DMF and were monitored by TLC; visualization was done with UV-light (254 nm).



Entry	Structure	Reaction time (h)	Yield (%)
12a		10	94
12b		8	91
12c		10	89

Entry	Structure	Reaction time (h)	Yield (%)
14a		14	92
14b		14	89
14c		16	90

Scheme 3.

4.1.1. 2-Amino-4-methyl-6-methylsulfanyl-isophthalonitrile 5a. A mixture of 5-methyl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-one **3a** (181 mg, 1 mmol), malononitrile **4** (1.2 mmol), and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 8 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 neutral alumina column using chloroform/hexane (1:9), which gave the title compound **5a** (181 mg, 89%) as a white solid; mp 236–238 °C; R_f ($CHCl_3$) 0.46; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H, Me), 2.54 (s, 3H, SMe), 5.10 (br s, 2H, NH_2), 6.42 (s, 1H, ArH); IR (KBr) 2213 (CN), 3353, 3442 (NH_2) cm^{-1}; MS (FAB) 204 (M^++1); HRMS calcd for $C_{10}H_9N_3S$: 203.0532, found: 203.0517.

4.1.2. 2-Amino-4-ethyl-6-methylsulfanyl-isophthalonitrile 5b. A procedure similar to the one described above for the preparation of **5a** starting from **3b** (195 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **5b** (189 mg, 87%) as a white solid; mp 146–148 °C; R_f ($CHCl_3$) 0.48; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J=7.6 Hz, 3H, Me), 2.56 (s, 3H, SMe), 2.73 (q, J=7.6 Hz, 2H, CH_2), 5.13 (br s, 2H, NH_2), 6.44 (s, 1H, ArH); IR (KBr) 2211 (CN), 3328, 3422 (NH_2) cm^{-1}; MS (FAB) 218 (M^++1).

4.1.3. 2-Amino-4-ethyl-5-methyl-6-methylsulfanyl-isophthalonitrile 5c. A procedure similar to the one described above for the preparation of **5a** starting from **3c** (209 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (10% $CHCl_3$/hexane) gave the title compound **5c** (208 mg, 90%) as a white solid; mp 202–204 °C; R_f ($CHCl_3$) 0.45; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, J=7.6 Hz, 3H, Me), 2.43 (s, 3H, Me), 2.51 (s, 3H, SMe), 2.86 (q, J=7.6 Hz, 2H, CH_2), 5.04 (br s, 2H, NH_2); IR (KBr) 2220 (CN), 3349, 3417 (NH_2) cm^{-1}; MS (FAB) 232 (M^++1).

4.1.4. 2-Amino-4-isopropyl-6-methylsulfanyl-isophthalonitrile 5d. A procedure similar to the one described above for the preparation of **5a** starting from **3d** (209 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **5d** (206 mg, 89%) as a white solid; mp 138–140 °C; R_f ($CHCl_3$) 0.48; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, J=6.8 Hz, 6H,

2Me), 2.57 (s, 3H, SMe), 2.75–2.86 (m, 1H, CH), 5.14 (br s, 2H, NH_2), 6.48 (s, 1H, ArH); IR (KBr) 2220 (CN), 3343, 3405 (NH_2) cm^{-1}; MS (FAB) 231 (M^++1); HRMS calcd for $C_{12}H_{13}N_3S$: 231.0830, found: 231.0797.

4.1.5. 2-Amino-4-isobutyl-6-methylsulfanyl-isophthalonitrile 5e. A procedure similar to the one described above for the preparation of **5a** starting from **3e** (223 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (10% $CHCl_3$/hexane) gave the title compound **5e** (223 mg, 91%) as a white solid; mp 164–166 °C; R_f ($CHCl_3$) 0.45; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, J=6.6 Hz, 6H, 2Me), 1.95–2.03 (m, 1H, CH), 2.55 (s, 3H, SMe), 2.62 (d, J=7.2 Hz, 2H, CH_2), 5.13 (br s, 2H, NH_2), 6.37 (s, 1H, ArH); IR (KBr) 2222 (CN), 3348, 3408 (NH_2) cm^{-1}; MS (FAB) 246 (M^++1); HRMS calcd for $C_{10}H_9N_3S$: 245.0987, found: 245.0983.

4.1.6. 2-Amino-4-isopropyl-6-morpholin-4-yl-isophthalonitrile 7a. A procedure similar to the one described above for the preparation of **5a** starting from **6a** (248 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (15% $CHCl_3$/hexane) gave the title compound **7a** (232 mg, 86%) as a white solid; mp 190–192 °C; R_f ($CHCl_3$) 0.40; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (d, J=6.8 Hz, 6H, $2CH_3$), 3.15–3.37 (m, 5H, CH and $2CH_2$), 3.83–3.91 (m, 4H, $2CH_2$), 5.10 (br s, 2H, NH_2), 6.17 (s, 1H, ArH); IR (KBr) 2210 (CN), 3353, 3412 (NH_2) cm^{-1}; MS (ESI) 271 (M^++1); HRMS calcd for $C_{13}H_{15}N_3S$: 270.1481, found: 270.1483.

4.1.7. 2-Amino-4-isopropyl-6-piperidin-1-yl-isophthalonitrile 7b. A procedure similar to the one described above for the preparation of **5a** starting from **6b** (246 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (14% $CHCl_3$/hexane) gave the title compound **7b** (247 mg, 92%) as a white solid; mp 150–152 °C; R_f ($CHCl_3$) 0.42; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, J=6.8 Hz, 6H, $2CH_3$), 1.58–1.69 (m, 2H, CH_2), 1.70–1.80 (m, 4H, $2CH_2$), 3.10–3.23 (m, 1H, CH), 3.29–3.37 (m, 4H, $2CH_2$), 5.02 (br s, 2H, NH_2), 6.15 (s, 1H, ArH); IR (KBr) 2212 (CN), 3350, 3411 (NH_2) cm^{-1}; MS (ESI) 269 (M^++1).

4.1.8. 2-Amino-4-isopropyl-6-(4-methyl-piperazin-1-yl)-isophthalonitrile 7c. A procedure similar to the one described above for the preparation of **5a** starting from **6c** (261 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (16% $CHCl_3$/hexane) gave the title compound **7c** (252 mg, 89%) as a white solid; mp 176–178 °C; R_f ($CHCl_3$) 0.39; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, J=6.8 Hz, 6H, $2CH_3$), 2.35 (s, 3H, NMe), 2.55–2.62 (m, 4H, $2CH_2$), 3.11–3.24 (m, 1H, CH), 3.33–3.41 (m, 4H, $2CH_2$), 5.07 (br s, 2H, NH_2), 6.15 (s, 1H, ArH); IR (KBr) 2213 (CN), 3355, 3408 (NH_2) cm^{-1}; MS (ESI) 284 (M^++1).

4.1.9. 4-Amino-2′-fluoro-2-methyl-6-methylsulfanyl-biphenyl-3,5-dicarbonitrile 10a. A procedure similar to the one described above for the preparation of **5a** starting from **9a** (275 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (10% $CHCl_3$/hexane) gave the title compound **10a** (279 mg, 94%) as a white solid; mp 192–194 °C; R_f ($CHCl_3$) 0.50; ^1H 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, 3413 (NH_2) cm^{-1}; 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.

4.1.10. 4-Amino-4′-fluoro-2-methyl-6-methylsulfanyl-biphenyl-3,5-dicarbonitrile 10b. A procedure similar to the one described above for the preparation of **5a** starting from **9b** (275 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (10% $CHCl_3$/hexane) gave the title compound **10b** (258 mg, 87%) as a white solid; mp 210–210 °C; R_f ($CHCl_3$) 0.48; ^1H 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), 7.06–7.22 (m, 4H, ArH); IR (KBr) 2219 (CN), 3334, 3452 (NH_2) cm^{-1}; MS (FAB) 298 (M^++1).

4.1.11. 4-Amino-2-methyl-6-methylsulfanyl-4′-trifluoromethyl-biphenyl-3,5-dicarbonitrile 10c. A procedure similar to the one described above for the preparation of **5a** starting from **9c** (325 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **10c** (312 mg, 90%) as a white solid; mp 122–124 °C; R_f ($CHCl_3$) 0.45; ^1H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.31 (s, 3H, SCH_3), 5.25 (br s, 2H, NH_2), 7.24–7.41 (m, 2H, ArH), 7.53–7.73 (m, 2H, ArH); IR (KBr) 2221 (CN), 3351, 3416 (NH_2) cm^{-1}; MS (FAB) 348 (M^++1); HRMS calcd for $C_{17}H_{12}F_3N_3S$: 347.0704, found: 347.0708.

4.1.12. 4-Amino-2′,4′-dimethoxy-2-methyl-6-methylsulfanyl-biphenyl-3,5-dicarbonitrile 10d. A procedure similar to the one described above for the preparation of **5a** starting from **9d** (317 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (11% $CHCl_3$/hexane) gave the title compound **10d** (302 mg, 89%) as a white solid; mp 206–208 °C; R_f ($CHCl_3$) 0.47; ^1H NMR (200 MHz, $CDCl_3$) δ 2.18 (s, 3H, CH_3), 2.28 (s, 3H, SCH_3), 3.73 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.15 (br s, 2H, NH_2), 6.52–6.61 (m, 2H, ArH), 6.88 (d, J=8.4 Hz, 1H, ArH); IR (KBr) 2218 (CN), 3348, 3424 (NH_2) cm^{-1}; MS (FAB) 340 (M^++1); HRMS calcd for $C_{18}H_{17}N_3O_2S$: 339.1041, found: 339. 1029.

4.1.13. 4-Amino-3′,4′-dimethoxy-2-methyl-6-methylsulfanyl-biphenyl-3,5-dicarbonitrile 10e. A procedure similar to the one described above for the preparation of **5a** starting from **9e** (317 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (10% $CHCl_3$/hexane) gave the title compound **10e** (308 mg, 91%) as a white solid; mp 212–214 °C; R_f ($CHCl_3$) 0.49; ^1H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 2.31 (s, 3H, SCH_3), 3.86 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.17 (br s, 2H, NH_2), 6.59–6.69 (m, 2H, ArH), 6.93 (d, J=8.0 Hz, 1H, ArH); IR (KBr) 2216 (CN), 3354, 3426 (NH_2) cm^{-1}; MS (FAB) 340 (M^++1); HRMS calcd for $C_{18}H_{17}N_3O_2S$: 339.1041, found: 339.1028.

4.1.14. 4-Amino-2-benzyl-6-methylsulfanyl-biphenyl-3,5-dicarbonitrile 10f. A procedure similar to the one described above for the preparation of **5a** starting from **9f** (333 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (14% $CHCl_3$/hexane) gave the title compound **10f**

(327 mg, 92%) as a white solid; mp 138–149 °C; R_f ($CHCl_3$) 0.44; ^1H NMR (200 MHz, $CDCl_3$) δ 2.28 (s, 3H, SCH_3), 3.95 (s, 2H, CH_2), 5.26 (br s, 2H, NH_2), 6.72–6.81 (m, 2H, ArH), 6.90–6.99 (m, 2H, ArH), 7.11–7.19 (m, 3H, ArH), 7.29–7.37 (m, 3H, ArH); IR (KBr) 2214 (CN), 3343, 3424 (NH_2) cm^{-1}; MS (FAB) 355 (M^++1).

4.1.15. 3-Amino-6-methyl-5-methylsulfanyl-biphenyl-2,4-dicarbonitrile 12a. A procedure similar to the one described above for the preparation of **5a** starting from **11a** (257 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **12a** (262 mg, 94%) as a white solid; mp 220–222 °C; R_f ($CHCl_3$) 0.45; ^1H 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, 3407 (NH_2) cm^{-1}; MS (FAB) 280 (M^++1); HRMS calcd for $C_{16}H_9N_3S$: 279.0830, found: 279.0846. 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.

4.1.16. 3-Amino-4′-chloro-6-methyl-5-methylsulfanyl-biphenyl-2,4-dicarbonitrile 12b. A procedure similar to the one described above for the preparation of **5a** starting from **11b** (291 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (10% $CHCl_3$/hexane) gave the title compound **12b** (285 mg, 91%) as a white solid; mp 200–202 °C; R_f ($CHCl_3$) 0.48; ^1H NMR (200 MHz, $CDCl_3$) δ 2.16 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 5.15 (br s, 2H, NH_2), 7.18 (d, J=8.2 Hz, 2H, ArH), 7.48 (d, J=8.2 Hz, 2H, ArH); IR (KBr) 2221 (CN), 3350, 3413 (NH_2) cm^{-1}; MS (FAB) 314 (M^++1); HRMS calcd for $C_{16}H_{12}ClN_3S$: 313.0440, found: 313.0450.

4.1.17. 3-Amino-4′-methoxy-6-methyl-5-methylsulfanyl-biphenyl-2,4-dicarbonitrile 12c. A procedure similar to the one described above for the preparation of **5a** starting from **11c** (287 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (13% $CHCl_3$/hexane) gave the title compound **12c** (275 mg, 89%) as a white solid; mp 188–190 °C; R_f ($CHCl_3$) 0.46; ^1H NMR (200 MHz, $CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.58 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 5.13 (br s, 2H, NH_2), 7.00 (d, J=8.0 Hz, 2H, ArH), 7.17 (d, J=8.0 Hz, 2H, ArH); IR (KBr) 2228 (CN), 3364, 3432 (NH_2) cm^{-1}; MS (FAB) 310 (M^++1); HRMS calcd for $C_{17}H_{15}N_3OS$: 309.0936, found: 309.0935.

4.1.18. 3-Amino-6-methyl-5-piperidin-1-yl-biphenyl-2,4-dicarbonitrile 14a. A procedure similar to the one described above for the preparation of **5a** starting from **13a** (294 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (15% $CHCl_3$/hexane) gave the title compound **14a** (291 mg, 92%) as a white solid; mp 210–212 °C; R_f ($CHCl_3$) 0.40; ^1H NMR (200 MHz, $CDCl_3$) δ 1.62–1.72 (m, 6H, $3CH_2$), 1.88 (s, 3H, CH_3), 3.25–3.34 (m, 4H, $2CH_2$), 5.02 (br s, 2H, NH_2), 7.20–7.24 (m, 2H, ArH), 7.44–7.50 (m, 3H, ArH); IR (KBr) 2218 (CN), 3346, 3409 (NH_2) cm^{-1}; MS (FAB) 316 (M^+); HRMS calcd for $C_{20}H_{20}N_4$: 316.1680, found: 316.1689.

4.1.19. 3-Amino-6-methyl-5-(4-methyl-piperidin-1-yl)-biphenyl-2,4-dicarbonitrile 14b. A procedure similar to the one described above for the preparation of **5a** starting from **13b** (308 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (13% $CHCl_3$/hexane) gave the title compound **14b** (293 mg, 89%) as a white solid; mp 192–194 °C; R_f ($CHCl_3$) 0.43; ^1H NMR (200 MHz, $CDCl_3$) δ 1.02 (d, J=6.2 Hz, 3H, CH_3), 1.30–1.43 (m, 2H, CH_2), 1.52–1.64 (m, 1H, CH), 1.70–1.79 (m, 2H, CH_2), 1.86 (s, 3H, CH_3), 3.26–3.34 (m, 4H, $2CH_2$), 5.04 (br s, 2H, NH_2), 7.17–7.22 (m, 2H, ArH), 7.42–7.50 (m, 3H, ArH); IR (KBr) 2219 (CN), 3341, 3411 (NH_2) cm^{-1}; MS (FAB) 330 (M^+).

4.1.20. 3-Amino-4′-chloro-6-methyl-5-piperidin-1-yl-biphenyl-2,4-dicarbonitrile 14c. A procedure similar to the one described above for the preparation of **5a** starting from **13c** (324 mg, 1 mmol), **4** (0.08 mL, 1.2 mmol) and chromatography (14% $CHCl_3$/hexane) gave the title compound **14c** (315 mg, 90%) as a white solid; mp 210–212 °C; R_f ($CHCl_3$) 0.41; ^1H NMR (200 MHz, $CDCl_3$) δ 1.62–1.68 (m, 6H, $3CH_2$), 1.87 (s, 3H, CH_3), 3.26–3.32 (m, 4H, $2CH_2$), 5.04 (br s, 2H, NH_2), 7.18 (d, J=8.0 Hz, 2H, ArH), 7.46 (d, J=8.0 Hz, 2H, ArH); IR (KBr) 2213 (CN), 3351, 3414 (NH_2) cm^{-1}; MS (FAB) 350 (M^+); HRMS calcd for $C_{20}H_{19}ClN_4$: 350.1298, found: 350.1297.

Acknowledgements

This work was supported by the Department of Science and Technology (DST), New Delhi. F.V.S. and V.K. thank Council of Scientific and Industrial Research, New Delhi, for research fellowships. Authors are thankful to SAIF, CDRI, Lucknow for providing spectroscopic data.

References and notes

1. (a) Sadek, K. U.; Selim, M. A.; Elmaghraby, M. A.; Elnagdi, M. H. *Pharmazie* **1993**, *48*, 419; (b) Hartke, K.; Sauerbier, M.; Richter, W. F. *Arch. Pharm. (Weinheim, Ger.)* **1992**, *325*, 279; (c) Gewald, K.; Schaefer, H. *Z. Chem.* **1981**, *21*, 183.
2. (a) Banzatti, C.; Mellini, P.; Salvadori, P. *Gazz. Chim. Ital.* **1987**, *117*, 259; (b) Dunn, J. P.; Ackerman, N. A.; Tomolonis, A. J. *J. Med. Chem.* **1986**, *29*, 2326; (c) Nakib, T.; Meegan, M. J.; Looney, A. M.; Burke, M. L. *Eur. J. Med. Chem.* **1992**, *27*, 971.
3. (a) Nakazato, A.; Ohta, K.; Sekiguchi, Y.; Okuyama, S.; Chaki, S.; Kawashima, Y.; Hatayama, K. *J. Med. Chem.* **1999**, *42*, 1076; (b) Nakazato, A.; Sekiguchi, Y.; Ohta, K.; Chaki, S.; Okuyama, S. *Bioorg. Med. Chem.* **1999**, *7*, 2027; (c) Boyle, E. A.; Mangan, F. R.; Markwell, R. E.; Smith, S. A.; Thomson, M. J.; Ward, R. W.; Wyman, P. A. *J. Med. Chem.* **1986**, *29*, 894; (d) Singh, F. V.; Vatsyanan, R.; Roy, U.; Goel, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2734.
4. (a) Victory, P.; Borrell, J. I.; Vidal-Ferran, A.; Montenegro, E.; Jimeno, M. L. *Heterocycles* **1993**, *36*, 2273; (b) Petersen, P. M.; Wu, W.; Fenlon, E. E.; Kim, S.; Zimmer, S. C. *Bioorg. Med. Chem.* **1996**, *4*, 1107.
5. Yu, Z.; Velasco, D. *Tetrahedron Lett.* **1999**, *40*, 3229.
6. (a) *Modern Arene Chemistry*; Astrue, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; (b) Xi, C.; Chen, C.; Lin, J.; Hong, X. *Org. Lett.* **2005**, *7*, 347; (c) Katritzsky, A. R.; Belyakov, S. A.; Henderson, S. A.; Steel, P. J. *J. Org. Chem.* **1997**, *62*, 8215; (d) Covarrubias-Zuniga, A.; Rios-Barrios, E. *J. Org. Chem.* **1997**, *62*, 5688.

7. (a) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240; (b) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
8. (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879; (b) Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430.
9. (a) Negishi, E. *Acc. Chem. Res.* **1982**, *11*, 413; (b) Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031; (c) Mitchell, T. N. *Synthesis* **1992**, 803; (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2497.
10. (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306; (b) Chauder, B.; Green, L.; Snieckus, V. *Pure Appl. Chem.* **1999**, *71*, 1521.
11. (a) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093; (b) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672.
12. (a) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187; (b) Wang, H.; Huang, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 8980; (c) Vorogushin, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Am. Chem. Soc.* **2002**, *124*, 6512.
13. (a) Xi, Z.; Sato, K.; Gao, Y.; Lu, J.; Takahashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 9568; (b) Takahashi, T.; Ishikawa, M.; Huo, S. *J. Am. Chem. Soc.* **2002**, *124*, 388.
14. (a) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921; (b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650; (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458.
15. (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901; (b) Bonaga, L. V. R.; Zhang, H.-C.; Moretto, A. F.; Ye, H.; Gauthier, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473.
16. Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 3128.
17. (a) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4033; (b) Katritzky, A. R.; Li, J.; Xie, L. *Tetrahedron* **1999**, *55*, 8263.
18. (a) Victory, P.; Alvarez-Larena, A.; Germain, G.; Kessels, R.; Piniella, J. F.; Vidal-Ferran, A. *Tetrahedron* **1995**, *51*, 235; (b) Murugan, P.; Shanmugasundaram, P.; Ramakrishnan, V. T.; Srividya, N.; Ramamurthy, P. *Indian J. Chem.* **1998**, *37B*, 737.
19. Khaidem, I. S.; Singh, S. L.; Singh, L. R.; Khan, M. Z. R. *Indian J. Chem.* **1996**, *35B*, 911.
20. (a) Woodward, B. T.; Posner, G. H. *Adv. Cycloaddit.* **1999**, *5*, 47; (b) Posner, G. H.; Afarinkia, K.; Dai, H. *Org. Synth.* **1995**, *73*, 231; (c) Afarinkia, K.; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2005**, *70*, 1122 and references cited therein.
21. (a) Goel, A.; Verma, D.; Dixit, M.; Raghunandan, R.; Maulik, P. R. *J. Org. Chem.* **2006**, *71*, 804; (b) Singh, F. V.; Kumar, A.; Goel, A. *Tetrahedron Lett.* **2006**, *47*, 7767; (c) Singh, F. V.; Kumar, V.; Goel, A. *Synlett* **2007**, 2086; (d) Singh, F. V.; Goel, A. *Tetrahedron Lett.* **2005**, *45*, 5585.
22. (a) Farhanullah; Agarwal, N.; Goel, A.; Ram, V. J. *J. Org. Chem.* **2003**, *68*, 2983; (b) Goel, A.; Singh, F. V.; Sharon, A.; Maulik, P. R. *Synlett* **2005**, 623.
23. Goel, A.; Singh, F. V.; Verma, D. *Synlett* **2005**, 2027.
24. Goel, A.; Singh, F. V.; Dixit, M.; Verma, D.; Raghunandan, R.; Maulik, P. R. *Chem. Asian J.* **2007**, *2*, 239.
25. (a) Tominaga, Y.; Ushirogochi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557; (b) Tominaga, Y. *Trends Heterocycl. Chem.* **1991**, *2*, 43.
26. (a) Torssell, K. G. B. *Natural Product Chemistry*; Wiley: Chichester, UK, 1983; (b) Thomson, R. H. *The Chemistry of Natural Products*; Blackie and Son: Glasgow, 1985.
27. (a) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187; (b) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556.
28. Mikes, F.; Boshart, G. *J. Chromatogr.* **1978**, *149*, 455.
29. (a) Yamamura, K.; Ono, S.; Tabushi, I. *Tetrahedron Lett.* **1988**, *29*, 1797; (b) Yamamura, K.; Ono, S.; Ogoshi, H.; Masuda, H.; Kuroda, Y. *Synlett* **1989**, 18.
30. (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
31. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
32. (a) Alberico, D.; Scott, M. E.; Luutens. *Chem. Rev.* **2007**, *107*, 104; (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 3541; (c) Goossen, L. G.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824; (d) Becht, J.-M.; Catala, C.; Drian, C. L.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.