Med Chem Res (2014) 23:2608–2614
DOI 10.1007/s00044-013-0857-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

DABCO-promoted one-pot synthesis of heteroaryl-substituted benzenes and their biological evaluation

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Received: 18 June 2013 / Accepted: 17 October 2013 / Published online: 27 October 2013

Abstract A simple and efficient one-pot synthesis of heteroaryl-substituted benzenes has been developed via cyclocondensation of vinylmalononitriles and ethylvinylcyanoacetates with heteroarylnitroolefines using diazabicyclo[2,2,2]octane as catalyst. The titled compounds were evaluated for their antitubercular, antibacterial and antifungal activities at various concentrations.

Keywords Heteroayl-substituted benzenes · DABCO · Antitubercular activity · Antibacterial activity · Antifungal activity

Introduction

Polysubstituted benzenes are highly useful compounds in organic chemistry, natural product chemistry and pharmaceutical chemistry. Polysubstituted benzenes also play important role in medicinal chemistry for the fact that they have common structural features in various bioactive molecules and are frequently employed as precursors for the synthesis of many bioactive heterocyclic compounds (Warshakoon *et al.*, 2006). Consequently enormous numbers of procedures have been developed for the construction of polysubstituted benzenes. Aromatic substitutions including Freidel–Crafts acylations and alkylations (Olah, 1963) nucleophilic substitutions (Hassan *et al.*, 2002), and coupling reactions (Saito and Yamamoto, 2000) based on the given aromatics are interpreted as traditional approaches. On the other hand, the approach to construct aromatic backbone from catenulate precursors has received growing interest not only due to the short sequence and regioselectivity, but also due to the advancement from the view point of atom economy (Trost, 1991) and environmental concern. These general features are common in the most useful benzannulation reactions such as the [4+2] cycloaddition of metalacyclopentadienes and alkynes (Xi *et al.*, 2003), transition metal catalysed [4+2] cycloadditions (Bonaga *et al.*, 2005), [5+1] benzannulation strategy between alkenoyl keteneacetals and nitro-alkane (Barun *et al.*, 2002), and [4+2] benzannulation of *O*-alkynyl benzaldehyde and alkyne (Asao *et al.*, 2003).

In general, it is difficult to introduce a heteroaryl group, nitrile and ester group to the given aromatics. Some methods were developed to synthesise the functionalized benzenes from acyclic compounds as follows: (i) Base-promoted cyclocondensation of arylethyldene and arylidene malononitriles and the elimination of nitrile group in succession, which provides 2-amino isophthalonitriles (Milart *et al.*, 1998). (ii) One-pot two-step tandem reaction of vinyl malononitriles and nitro olefins promoted by two different kinds of bases for each step, which obtains a series of substituted 2-amino-3-nitro benzonitriles (Xue *et al.*, 2007), and (iii) one-pot synthesis of 2-amino-3-nitro-benzonitriles and 2-amino-3-nitro benzoates by the condensation of activated-methylene alkenes with nitro olefins using $Cu(OTf)_2/Et_3N$ (Weike *et al.*, 2009). But, these methods often suffer from certain drawbacks such as long playing procedures, hazardous by products, use of stoichiometric or even excess amount of base and use of metal triflates. Therefore, to synthesise poly substituted benzenes efficiently and catalytically is an important task in organic synthesis.

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Therefore, in continuation of our interest towards the using of diazabicyclo-[2,2,2]-octane (DABCO) in various organic syntheses (Jain *et al.*, 2012a, 2013) herein we are reporting a new synthetic method for the synthesis of heteroaryl-substituted benzenes using vinylmalononitriles, obtained from ketones via a Knoevenagel reaction with heteroarylnitroolefins in the presence of DABCO as base and CH_3CN as the solvent via one-pot tandem addition process. This introduces a new strategy for the synthesis of heteroaryl-substituted aromatic compounds using heteroarylnitroolefins as the starting materials.

Physical properties of DABCO

(a) *Appearance* solid
(b) *Colour* white
(c) *Odour* no specific
(d) *Melting range* 156–159 °C
(e) *Boiling range* 174 °C
(f) *Vapour pressure* 3.9 hPa at 50 °C
(g) *Relative density* 1.02 g/mL at 25 °C
(h) *Water solubility* soluble
(i) *Molecular formula* $C_6H_{12}N_2$

Results and discussion

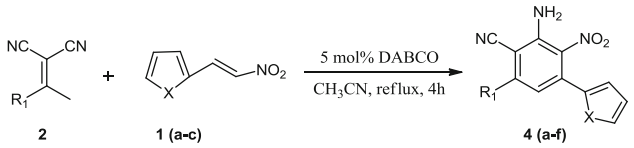
In order to optimise the reaction conditions, the synthesis of compound **4c** (Table 2) was used as a model reaction. Therefore, the reaction was carried out by stirring a mixture of vinyl malono nitrile **2** (2 mmol), heteroarylnitroolefin **1c** (2 mmol) and CH_3CN in different amounts of DABCO (Table 1). The efficiency of the reaction is mainly affected by the amount of the catalyst. No product could be detected in the absence of the catalyst even after 12 h (entry 1), while good results were obtained in the presence of DABCO. The optimal amount of the catalyst was 5 mol% (entry 3), the higher amount of the catalyst did not increase the yield noticeably (entry 6).

Table 1 Effect of different concentrations of catalyst for the synthesis of heteroaryl-substituted benzenes

Entry	Catalyst	Catalyst loading (mol%)	Time (h)	Yield (%)[b]
1	No catalyst	–	12[a]	–
2	DABCO	1	7	64
3	DABCO	5	5	76
4	DABCO	10	4	88
5	DABCO	15	4	88
6	DABCO	20	3.5	86

[a] No change observed even after prolonged stirring up to 12 h

[b] Isolated yields



Scheme 1 Synthesis of 2-amino-3-nitro-6-heteroarylbenzonitriles (**4a–f**)

In our initial study, we observed that vinyl malononitriles **2**(**a–f**) could undergo cyclocondensation with heteroarylnitroolefins **1**(**a–c**) in the presence of 5 mol% of DABCO (Scheme 1). The reaction was carried out under air. Acetonitrile was chosen as solvent due to solubility of all starting materials. The products, a series of 2-amino-3-nitro-4-heteroarylbenzonitriles **4**(**a–f**) are obtained in good yields. The details are summarised in (Table 2).

To extend the scope of the reaction, other activated alkenes, such as Knoevenagel condensed products of ketones with ethylcyanoacetate **3**(**a–f**), were made to react with heteroaryl nitroolefins **1**(**a–c**) using the present protocol (Scheme 2). The products were obtained in moderate yields. The details are summarised in Table 3.

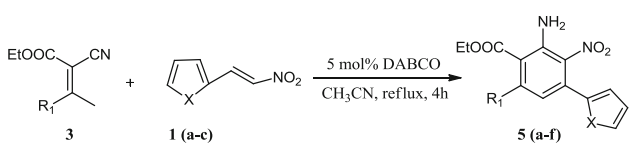
In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of heteroaryl-substituted benzenes in the presence of K_2CO_3, $Cu(OTf)_2/Et_3N$, EtONa, GIL and Pyridine with DABCO with respect to the reaction times and yield of the product (Table 4). However, reaction

Table 2 DABCO-promoted synthesis of 2-amino-3-nitro-6-heteroarylbenzonitriles (**4a–f**)

Entry	R_1	X	DABCO (mol%)	Time (h)	Product	Yield (%)[a]	M.p. (°C)
1	C_6H_5	NH	5	5	**4a**	74	211–218
2	C_6H_5	S	5	4.5	**4b**	84	189–191
3	C_6H_5	O	5	4	**4c**	88	273–275
4	4-OMe–C_6H_4	NH	5	4	**4d**	70	226–229
5	4-OMe–C_6H_4	S	5	5	**4e**	84	201–203
6	4-OMe–C_6H_4	O	5	4.5	**4f**	80	243–245

Vinyl malanonitrile (2 mmol), heteroarylnitroolefin (2 mmol) and 5 mol% DABCO in CH_3CN under reflux temperature

[a] Isolated yields



Scheme 2 Synthesis of ethyl-2-amino-3-nitro-4-heteroarylbenzoates (**5a–f**)

in the presence of these catalysts required longer reaction times than DABCO.

Based on the experimental results, a plausible reaction mechanism is illustrated (Scheme 3). The reaction involves the Michael addition of activated alkenes with heteroarylnitroolefins, the cyclisation catalysed by 5 mol% DABCO, and the oxidation takes place in atmosphere to form heteroaryl-substituted benzene.

Table 3 DABCO-promoted synthesis of ethyl-2-amino-3-nitro-4-heteroarylbenzoates (**5a–f**)

Entry	R_1	X	DABCO (mol%)	Time (h)	Product	Yield (%)[a]	M.p. (°C)
1	C_6H_5	NH	5	5.5	**5a**	62	203–205
2	C_6H_5	S	5	6	**5b**	65	195–197
3	C_6H_5	O	5	5	**5c**	61	291–293
4	4-OMe–C_6H_4	NH	5	5	**5d**	57	231–233
5	4-OMe–C_6H_4	S	5	5.5	**5e**	64	213–215
6	4-OMe–C_6H_4	O	5	5	**5f**	68	257–259

Ethylvinylcyanoacetate (2 mmol), heteroarylnitroolefin (2 mmol), and 5 mol% DABCO in CH_3CN under reflux temperature

[a] Isolated yields

Table 4 Comparison of our results with earlier reported methods

Entry	Catalyst	Conditions	Time (h)	Yield (%)[a,b]
1	K_2CO_3	DMF/RT	16	67[c]
2	$Cu(OTf)_2/Et_3N$	DMF/reflux	6	72[d]
3	EtONa	CH_3CN/reflux	8	78[e]
4	GIL	H_2O/reflux	7	57[f]
5	Pyridine	MW/159W, 100 °C	10 min	63[g]
6	DABCO	CH_3CN/reflux	4	88[h]

[a] Jain *et al.* (2012c)

[b] Chen *et al.* (2011)

[c] Kim *et al.* (2008)

[d] Weike *et al.* (2009)

[e] Xue *et al.* (2007)

[f] Xin *et al.* (2010)

[g] Krishna and Satish (2010)

[h] This work

The antitubercular data (Table 5) revealed that the synthesised heteroaryl-substituted benzenes **4**(**a–c**) and **5**(**d–f**) proved to be active against *Mycobacterium tuberculosis* $H_{37}Rv$ strain at 100, 10 and 1 μg/mL levels. The antibacterial data (Table 6) shows that the product **4a** and **5e** displayed broad-spectrum activity, whereas **4c** and **5d** showed moderate activity and **4b** and **5f** showed poor activity against tested bacteria. The antifungal data (Table 7) show that the product **5e** displayed broad-spectrum activity against *Candida tropicalis*, **4a** and **4b** against *Candida albicans* and **4c** and **5e** against both *Aspergillus flavus and C. albicans*. It is clear that compounds **5e** and **4a–c** possess high activity, while rest of the products possesses moderate activity.

Experimental

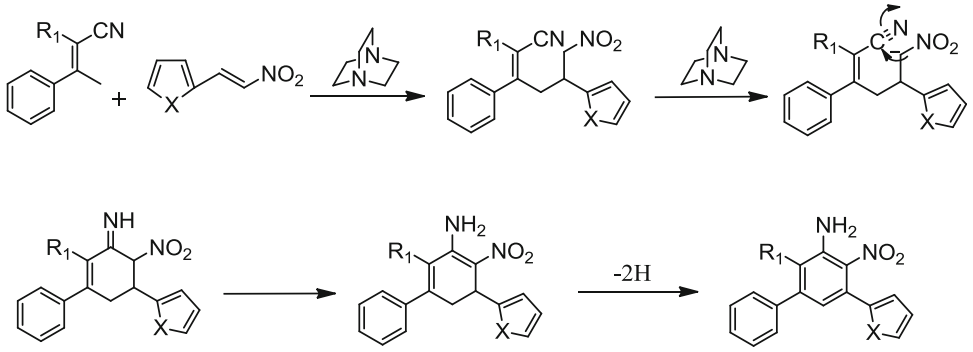
General

Melting points were measured on an Electro thermal 9100 apparatus and were uncorrected. All chemicals were purchased from Merck and Fluka used without further purification. ^{1}H-NMR spectra were obtained on a Bruker DRX-400 and ^{13}C-NMR spectra on a Bruker DRX-125 Advance spectrometer. FT-IR spectra were recorded on a Shimadzu FT-IR-8400S spectrometer. Chemical shifts of ^{1}H and ^{13}C-NMR spectra were expressed in ppm in downfield from tetramethylsilane. Antitubercular activity was tested against *M. tuberculosis* $H_{37}Rv$ strain using Lowenstein–Jensen medium method. Antibacterial and antifungal susceptibility test was done by disc diffusion method.

General procedure for the synthesis of 2-amino-3-nitro-4-heteroarylbenzonitriles (**4a–f**)

To a mixture vinyl malononitrile **2** (2 mmol) and heteroarylnitroolefin **1** (2 mmol) in CH_3CN (15 mL), DABCO (5 mol%) was added. The reaction mixture was stirred at reflux for 4 h. After completion of the reaction, EtOAc

Scheme 3 A plausible mechanism for the preparation of heteroaryl-substituted benzene



(15 mL) was added to dilute the reaction solution. Then, the mixture was washed with water and brine. The combined organic phases were dried and concentrated under vacuum, and the residue was purified by column chromatography (hexanes: EtOAc) to afford compound **4.**

General procedure for the synthesis of ethyl 2-amino-3-nitro-4-heteroarylbenzoates (**5a–f**)

To a mixture of **3** (2 mmol) and heteroarylnitroolefin **1** (2 mmol) in CH_3CN (15 mL), DABCO (5 mol%) was added. The reaction mixture was stirred at reflux for 4 h. After completion of the reaction, EtOAc (15 mL) was added to dilute the reaction solution. Then, the reaction mixture was washed with water and brine. The combined organic phases were dried and concentrated under vacuum, and the residue was purified by column chromatography (hexanes: EtOAc) to afford compound **5.**

Table 5 Antitubercular activity data of heteroaryl-substituted benzenes

Compound	Concentration (μg/mL)		
	Mycobacterium tuberculosis		
	100	10	1
Control	++	++	++
Pyrazinamide	−ve	−ve	−ve
4a	−ve	−ve	−ve
4b	−ve	−ve	−ve
4c	−ve	−ve	−ve
5d	−ve	−ve	−ve
5e	−ve	−ve	−ve
5f	−ve	−ve	−ve

"++" indicates intensive growth of *M. tuberculosis*

"−ve" indicates complete inhibition of $H_{37}Rv$

Microbiology

Antitubercular evaluation

Newly synthesised compounds **4(a–c)** and **5(d–f)** were screened for antitubercular activity against *M. tuberculosis* $H_{37}Rv$ strain using Lowenstein–Jensen medium method (Cambau *et al.*, 2000; Jain *et al.*, 2012b, 2013). Ten milligram of each synthesised compound was dissolved in 10 mL of dimethyl sulphoxide (DMSO) to get a concentration of 1,000 μg/l. Further dilutions were made with DMSO to get different concentrations such as 100, 10 and 1 μg/mL. 0.8 ml of each concentration was used for the study. To this, 7.2 ml of Lowenstein–Jensen medium was added.

Pyrazinamide was used as the standard drug. The dilution of pyrazinamide was made with DMSO to get different concentrations of 100, 10 and 1 μg/mL. 0.8 ml of each concentration was used for the study. A sweep from the *M. tuberculosis* $H_{37}Rv$ culture was discharged with the help of nichrome wire loop with a 3 mm external diameter, into a

Table 6 Antibacterial activity of heteroaryl-substituted benzenes (zone of inhibition in mm)

Entry	Compound	*Escherichia coli*	*Salmonella typhi*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
1	Ciprofloxacin	22	24	22	23
2	Control	++	++	++	++
3	**4a**	14	24	18	16
4	**4b**	12	9	8	10
5	**4c**	17	16	12	14
6	**5d**	10	14	16	12
7	**5e**	14	16	20	18
8	**5f**	10	7	9	8

Minimum inhibitory concentration is 20 μg/mL

"++" indicates no zone of inhibition

Table 7 Antifungal activity of heteroaryl-substituted benzenes (zone of inhibition in mm)

Entry	Compound	*Candida albicans*	*Candida tropicalis*	*Aspergillus flavus*	*Aspergillus niger*
1	Clotrimazole	20	21	19	23
2	Control	++	++	++	++
3	**4a**	18	12	16	20
4	**4b**	24	21	12	15
5	**4c**	10	8	14	8
6	**5d**	9	10	12	10
7	**5e**	16	42	14	18
8	**5f**	7	8	9	10

Minimum inhibitory concentration is 20 μg/mL

"++" indicates no zone of inhibition

sterile distilled bijou bottle containing 6 mm glass beads and 4 mL of sterile distilled water. The bottle was shaken with the help of a mechanical shaker for 2 min, and then using nichrome wire loop, 3 mm external diameter, a loopful of suspension was inoculated on the surface of each of Lowenstein–Jensen medium containing the test compounds. Lowenstein–Jensen medium containing pyrazinamide as well as control were inoculated with *M. tuberculosis* $H_{37}Rv$ strain. The inoculated medium was incubated at 37 °C for 4 weeks. At the end of 4 weeks, readings were taken and recorded in (Table 6).

Antibacterial evaluation

The sensitivity of the bacteria isolated to the test compounds were done by agar-diffusion techniques (Mehta and Patel, 2006) stock solution at a concentration 10 mg/mL of each compound was prepared in DMSO. Twenty microlitre of each of the solution was adsorbed on sterile 6 mm Whatmann filter paper (#4) discs and kept for few hours under vacuum to remove the solvent.

Grown cultures were stored in trypticase soya broth oxide maintaining the pH 7.3 in 0.5 % agar at 4 °C in the screw capped tubes. Trypticase soya agar (DIFCO) plates were inoculated with standard suspension of different bacterial cultures containing 10^7 cfu/mL using sterile cotton swabs to obtain a confluent lawn. The prepared discs were placed on the surface at different positions and plates were incubated at 37 °C for 24 h. The results were recorded by measuring the zones of inhibition in mm against each compound (Table 6).

Antifungal evaluation

The antifungal activity of compounds **4**(**a**–**c**) and **5**(**d**–**f**) was studied against four fungal cultures. Saboraud's dextrose-agar was seeded with 10^5 cfu/mL (colony forming units) fungal spore suspension and transferred to petriplates. Twenty microlitre (10 mg/mL) of all compound solutions were impregnated into discs of 6 mm diameter. And the discs were kept under vacuum for few hours to evaporate solvent. Then the discs were placed at different positions on agar surface. The plates were incubated at 37 °C for 7 days. The results were recorded as zones of inhibition in mm against each compound (Table 7).

Spectral data

*3-Amino-4-nitro-5-(1H-pyrrole-2-yl)-[1,1′-biphenyl]-2-carboxylate (**4a**)*

Pale yellow powder, mp. 211–214 °C; IR (KBr) υ_{max}/cm^{-1}: 3397, 3329, 3215, 2196, 1660, 1469, 1363 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 4.86 (*s*, 1H), 5.69–5.70 (*d*, 2H), 6.47 (*d*, 1H), 6.732–6.750 (*t*, 2H), 7.23–7.39 (*m*, 6H), 7.26 (*s*, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 94.1 (C–CN), 119.2 (CN), 129.2 (Ar–C), 132.1 (C–HetAr), 134.0 (C–NO_2), 142.6 (C–NH_2) and 148.6 (C–C_6H_5); FABMS *m/z* (% of abundance): 159 (100 %), 227 (58 %), 305 (44 %, M^+), 306 (28 %, M^++1), and 307 (20 %, M^++2); $C_{17}H_{12}N_4O_2$ (304.30): Calcd. C, 67.10; H, 3.97; N, 18.41; O, 10.52; Found. C, 67.11; H, 3.95; N, 18.43; O, 10.54.

*3-Amino-4-nitro-5-(thiophen-2-yl)-[1,1′-biphenyl]-2-carbonitrile (**4b**)*

White powder, mp. 189–191 °C; IR (KBr) υ_{max}/cm^{-1}: 3408, 3311, 2214, 1558, 1387 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 5.751 (*s*, 2H), 7.26 (*s*, 1H), 7.17–7.33 (*m*, 6H), and 7.62–7.90 (*m*, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 93.6 (C–CN), 116.3 (CN), 128.0 (Ar–C), 128.45 (C–HetAr), 132.3 (C–NO_2), 141.3 (C–NH_2), and 156.4 (C–C_6H_5); FABMS *m/z* (% of abundance): 136 (72 %), 155 (63 %), 237 (100 %), 321 (31 %, M^+), 322 (20 %, M^++1), and 323 (10 %, M^+ +2); $C_{17}H_{11}N_3O_2S$ (321.35); Calcd. C, 63.54; H, 3.45; O, 9.96; *s*, 9.99; N, 13.08; Found. C, 63.55; H, 3.65; O, 9.96; *s*, 9.99; N, 13.07.

*3-Amino-5-(furan-2-yl)-4-nitro-[1,1′-biphenyl]-2-carbonitrile (**4c**)*

Off white powder, mp. 273–275 °C; IR (KBr) υ_{max}/cm^{-1}: 3407, 3328, 2192, 1560, 1370 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 5.12 (*s*, 2H), 7.18–7.23 (*q*, 3H), and 7.28–7.38 (*m*, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 96.3 (C–CN), 114.8 (CN), 129.2 (C–HetAr), 129.4 (Ar–C), 132.1 (C–NO_2), 142.6 (C–NH_2), and 161.1 (C–C_6H_5); FABMS *m/z* (% of abundance):136 (75 %), 182 (50 %), 227 (100 %), 238 (59 %), 307 (26 %, M^+), and 308 (11 %, M^++1); $C_{17}H_{11}N_3O_2S$ (305.29); Calcd. C, 66.88; H, 3.63; N, 13.76; O, 15.72; Found. C, 66.87; H, 3.62; N, 13.77; O, 15.73.

*3-Amino-4′-methoxy-4-nitro-5-(1H-pyrrol-2-yl)-[1,1′-biphenyl-2-carbonitrile (**4d**)*

Pale brown powder, mp. 226–229 °C; IR (KBr) υ_{max}/cm^{-1}: 3397, 3328, 2965, 2196, 1661, 1503, 1363 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.79 (*s*, 3H), 4.13 (*s*, 1H), 4.82–4.85 (*t*, 2H), 6.82–6.84 (*d*, 2H), 7.08–7.11 (*d*, 1H), and 7.26–7.39 (*q*, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 55.2 (OCH_3), 97.2 (C–CN), 117.7 (CN), 123.2 (Ar–C), 129.5 (C–HetAr), 134.2 (C–NO_2), 137.6 (C–NH_2) and 153.3 (C–C_6H_5); FABMS *m/z* (% of abundance): 154 (75 %), 169 (70 %), 212 (92 %), 267 (100 %), 335 (38 %, M^+), 336 (22 %, M^++1), and 337 (8 %, M^++2).

$C_{18}H_{14}N_4O_3$ (334.33); Calcd. C, 64.66; H, 4.22; N, 16.76; O, 14.36; Found. C, 64.65; H, 4.23; N, 16.74; O, 14.38.

*3-Amino-4′-methoxy-4-nitro-5-(thiophen-2-yl)-[1,1′-biphenyl]-2-carbonitrile (**4e**)*

Pale yellow powder, mp. 201–203; IR (KBr) υ_{max}/cm^{-1}: 3370, 3115, 2226, 1513, 1420, 1397 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.57–2.60 (*t*, 2H), 3.88 (*s*, 3H), 7.10–7.13 (*m*, 5H), and 7.69–7.88 (*m*, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 56.9 (OCH_3), 96.6 (C–CN), 112.8 (CN), 124.9 (Ar–C), 127.3 (C–HetAr), 128.7 (C–NO_2), 140.4 (C–NH_2) and 155.5 (C–C_6H_5) FABMS *m/z* (% of abundance): 109 (63 %), 140 (60 %), 243 (100 %), 267 (42 %), 350 (46 %, M^+), 351 (38 %, M^++1), and 352 (20 %, M^++2); $C_{18}H_{13}N_3O_3S$ (351.38); Calcd. C, 61.53; H, 3.73; O, 13.66; S, 9.13; N, 11.96; Found. C, 61.52; H, 3.74; O, 13.67; S, 9.13; N, 11.95.

*3-Amino-5-(furan-2-yl)-4′-methoxy-4-nitro-5-[1,1′-biphenyl]-2-carbonitrile (**4f**)*

Brownish powder, mp. 243–245 °C; IR (KBr) υ_{max}/cm^{-1}: 3385, 3317, 3033, 2217, 1492, 1345 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.28 (*s*, 3H), 4.67 (*s*, 2H), 6.31–6.32 (*q*, 1H), 6.65–6.68 (*t*, 2H) and 7.22–7.33 (*m*, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 57.7 (OCH_3), 91.1 (C–CN), 114.4 (CN), 126.3 (Ar–C), 127.62 (C–HetAr), 128.3 (C–NO_2), 142.3 (C–NH_2) and 156.3 (C–C_6H_5); FABMS *m/z* (% of abundance): 123 (39 %), 140 (60 %), 154 (53 %), 230 (60 %), 303 (100 %), 335 (41 %, M^+), and 336 (24 %, M^++1); $C_{18}H_{13}N_3O_4$ (335.31); Calcd. C, 64.47; H, 3.91; N, 12.53; O, 19.09; Found. C, 64.48; H, 3.90; N, 12.52; O, 19.10.

*Ethyl-3-amino-4-nitro(1H-pyrrol-2-yl)-[1,1′-biphenyl]-2-carboxylate (**5a**)*

Off white powder, mp. 203–205 °C; FT-IR (neat) (ν_{max}/cm^{-1}): 3165, 3100, 1754, 1590, 1550, 1524, 1325, 756; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.372–1.392 (*s*, 3H), 4.327–4.347 (*d*, 2H), 6.1 (*s*, 2H), 7.124–7.242 (*m*, 2H), 7.4–7.5 (*m*, 6H), 8.280 (*s*, 1H), 9.7 (*s*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 14.1 (CH_3), 60.6 (–CH_2–), 127.7 (Ar–C), 130.6 (C–HetAr), 132.1 (C–NO_2), 140.8 (C–NH_2), and 168.9 (C=O); $C_{19}H_{17}N_3O_4$ (351.36); Calcd. C, 64.95; H, 4.88; N, 11.96; O, 18.21; Found. C, 64.92; H, 4.89; N, 11.94; O, 18. 20.

*Ethyl-3-amino-4-nitro(thiphen-2-yl)-[1,1′-biphenyl]-2-carboxylate (**5b**)*

Pale brown powder, mp. 195–197 °C; FT-IR (neat) (ν_{max}/cm^{-1}): 3429, 3118, 1723, 1675, 1276, 1109, 975, 870, 678; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.32 (*t*, 3H), 4.38 (*q*, 2H), 5.630 (*s*, 1H), 7.189–7.426 (*m*, 6H), 7.624–7.904 (*m*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 14.3 (CH_3), 62.0 (–CH_2–), 128.0 (Ar–C), 129.2 (C–HetAr), 137.4 (C–NO_2), 141.2 (C–NH_2), and 169.7 (C=O); $C_{19}H_{16}N_2O_4S$ (368.41); Calcd. C, 61.94; H, 4.38; N, 7.60; O, 17.37; S, 8.70; Found. C, 61.96; H, 4.35; N, 7.62; O, 17.35; S, 8.67.

*Ethyl-3-amino-4-nitro(furan-2-yl)-[1,1′-biphenyl]-2-carboxylate (**5c**)*

Off white powder, mp. 291–293 °C; FT-IR (neat) (ν_{max}/cm^{-1}): 3947, 3828, 3462, 3121, 1747, 1690, 1268, 1119, 714; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.362–1.382 (*t*, 3H), 4.372–4.392 (*q*, 2H), 5.230 (*s*, 1H), 7.180–7.225 (*q*, 3H), 7.278–7.376 (*m*, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 14.3 (CH_3), 61.2 (–CH_2–), 127.5 (Ar–C), 130.2 (C–HetAr), 137.5 (C–NO_2), 141.9 (C–NH_2), and 168.5 (C=O); $C_{19}H_{16}N_2O_5$ (352.34); Calcd. C, 64.77; H, 4.58; N, 7.95; O, 22.79; Found. C, 66.79; H, 4.53; N, 7.98; O, 22.76.

*Ethyl-3-amino-4′-methoxy-4-nitro-5-(1H-pyrrol-2-yl)-[1,1′-biphenyl-2-carbonitrile (**5d**)*

Pale green powder, mp. 231–233 °C; FT-IR (neat) (ν_{max}/cm^{-1}): 3402, 3214, 3126, 2942, 1763, 1690, 1276, 1109, 741; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.382–1.422 (*t*, 3H), 3.762 (*s*, 3H), 4.360–4.380 (*q*, 2H), 4.152 (*s*, 1H), 5.160 (*s*, 2H), 6.840–6.902 (*dd*, 2H), 7.108–7.120 (*d*, 1H), 7.272–7.405 (*m*, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 14.4 (CH_3), 55.9 (OCH_3), 60.9 (–CH_2–), 128.3 (Ar–C), 129.8 (C–HetAr), 137.2 (C–NO_2), 142.9 (C–NH_2), and 168.3 (C=O); $C_{20}H_{19}N_3O_5$ (381.38); Calcd. C, 62.99; H, 5.02; N, 11.02, O, 20.98; Found. C, 62.96; H, 5.05; N, 11.00; O, 20.99.

*Ethyl-3-amino-4′-methoxy-4-nitro-5-(thiophen-2-yl)-[1,1′-biphenyl-2-carbonitrile (**5e**)*

Off white powder, mp. 213–215 °C; FT-IR (neat) (ν_{max}/cm^{-1}): 3429, 3108, 1601, 1498, 1276, 1041, 755, 672; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.360 (*t*, 3H), 2.621–2.652 (*t*, 2H), 3.920 (*s*, 3H), 4.350–4.370 (*q*, 2H), 7.116–7.143 (*m*, 5H), 7.712–7.890 (*m*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 14.5 (CH_3), 56.0 (OCH_3), 60.3 (–CH_2–), 127.7 (Ar–C), 129.6 (C–HetAr), 137.3 (C–NO_2), 142.0 (C–NH_2), and 166.2 (C=O); $C_{20}H_{18}N_2O_5S$ (398.43); Calcd. C, 60.29; H, 4.55; N, 7.03; O, 20.08; S, 8.05; Found. C, 60.31; H, 4.52; N, 7.05; O, 20.05; S, 8.07.

*Ethyl-3-amino-4′-methoxy-4-nitro-5-(furan-2-yl)-[1,1′-biphenyl-2-carbonitrile (**5f**)*

Greenish powder, mp. 257–259 °C; FT-IR (neat) (ν_{max}/cm^{-1}): 3429, 3214, 3121, 3108, 1723, 1609, 1264,

1041, 760; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.390–1.420 (*t*, 3H), 3.264 (*s*, 3H), 4.362–4.392 (*q*, 2H), 4.68 (*s*, 2H), 6.315–6.327 (*q*, 1H), 6.654–6.694 (*m*, 2H), 7.286–7.383 (*m*, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 14.6 (CH_3), 56.3 (OCH_3), 62.1 (–CH_2–), 128.4 (Ar–C), 130.8 (C–HetAr), 137.9 (C–NO_2), 142.7 (C–NH_2), and 166.2 (C=O); $C_{20}H_{18}N_2O_6$ (382.37); Calcd. C, 62.82; H, 4.74; N, 7.33; O, 25.11; Found. C, 62.84; H, 4.72; N, 7.35; O, 25.09.

Conclusion

In conclusion, we have developed a new and efficient method for the synthesis of heteroaryl-substituted benzenes catalysed by DABCO. This provides a new strategy for the synthesis of heteroaryl-substituted benzenes using ketones and heteroaryl aldehydes as the starting materials. The synthesised compounds shown to have good antitubercular, antibacterial and antifungal activities.

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