A mild and practical synthesis of biphenyl compounds

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A mild and practical synthetic route for biphenyls is established. Isopropyl nitrite was prepared from sodium nitrite, isopropanol and hydrochloric acid. The biphenyl compounds were obtained from the diazotisation of aniline derivatives with the generated isopropyl nitrite and the coupling reaction with benzene derivatives in the presence of CuCl as a catalyst in good yields.

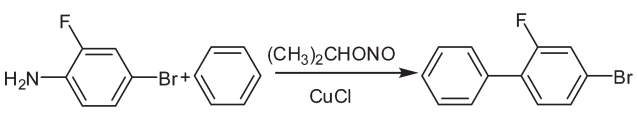
Keywords: biphenyls, aniline derivative, isopropyl nitrite, diazotisation

The biphenyl group is one of the most important substructures in a number of bioactive and functional molecules. It is used in many pharmaceutically active ingredients such as antibiotics, anti-inflammatory, antihypertensive, anticancer, antihistaminic and infertility treatments.[1–4] Moreover, the benzene–benzene bond is present in numerous natural products as well as in biologically active agrochemicals.[5] As a result, they have attracted considerable interest. There are numbers of synthetic routes for biphenyl compounds, and a wide variety of applications of these methods have been reviewed.[6–10] Among these methods, the classical Ullmann reaction is well known as constructing biphenyl frameworks from aryl halides in the presence of copper, but it requires harsh reaction conditions and has reputation for erratic yields.[11–18] Catalytic coupling reactions are also well known in biphenyl synthesis, such as Kharasch,[19] Negishi,[20] Stille[21] and Suzuki[22] reactions. Some of these synthetic methods have been applied in the industrial production. Nevertheless, there are some limitations to these synthetic methods, *e.g.* complex work-ups, dangerous or expensive and instable catalysts.

Recently, our group has focused on the synthesis of 2-fluoro-4-bromobiphenyl, which is a versatile and functional intermediate for synthesising flurbiprofen from 2-fluoro-4-bromoaniline and benzene (Scheme 1).[23] We found that 2-fluoro-4-bromobiphenyl can be generated in good (75.4%) yield by using isopropyl nitrite as the diazotising reagent. Compared with the traditional method of using sodium nitrite as the diazotising reagent, which was initially used to achieve the target molecule, the route reported here has several advantages such as mild conditions, simplified work-ups and low cost. This has triggered our interest in investigating the applicability of isopropyl nitrite as the diazotising reagent in the benzene–benzene coupling reaction. The obtained results are summarised and reported here.

Results and discussions

As isopropyl nitrite is volatile and potentially explosive, it should be used immediately after preparation. The isopropyl nitrite was obtained from the reaction of isopropanol, sodium nitrite and hydrochloric acid in water at 0–5 °C.The aniline derivative **1a** was diazotised with the generated isopropyl nitrite, followed by the coupling reaction with 1,4-dimethylbenzene in the presence of CuCl as a catalyst at room temperature to yield the corresponding biphenyl compound **2a** in moderate (46%) yield. Considering that there was some water in the generated isopropyl nitrite and the diazonium salt may transfer into the aqueous phase, which was negative for the coupling reaction, the organic phase containing isopropyl nitrite was separated from the reaction liquid and used in the next coupling reaction. Using the same molar ratio as above, the isolated yield of the improved experiment was increased to 64%.



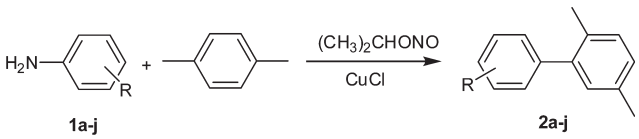
Scheme 1 Reaction of 2-fluoro-4-bromoaniline with isopropyl nitrite in benzene.

To demonstrate the generality of this benzene–benzene coupling reaction, a number of aniline derivatives with electron releasing and electron withdrawing groups at different positions **1a–j** were chosen for this reaction. The results are summarised in Table 1. It is clear that all of aniline derivatives except for **1g** and **1i** proceed effectively to obtain desired products in moderate or good yields. The steric hindrance can be the main reason that contributed to the failure of synthesising the corresponding target biphenyl compounds from **1g** and **1i**. In addition, it is attractive that the yields of aniline derivatives with electron-withdrawing groups are higher than those of aniline derivatives with electro-releasing groups.

In summary, we established a mild and practical method for synthesising biphenyl compounds using isopropyl nitrite to diazotise aniline derivatives at room temperature. In addition, numbers of biphenyl compounds were obtained with moderate to good yields by this method. This synthetic route has many advantages including mild conditions, simplified work-ups and low cost.

Experimental

Reagents and solvents were obtained from commercial suppliers. All reactions were carried out in air and monitored by TLC using commercial aluminium-backed silica gel plates. Melting points were observed on YRT-3 Melting Point Tester and are uncorrected. NMR



Scheme 2 Reaction of aniline derivatives with isopropyl in 1, 4-dimethylbenzene.

Table 1 Reactions of aniline derivatives with isopropyl nitrite in 1,4-dimethylbenzene

Entry	R=	Product
1	**1a** H	**2a**
2	**1b** 2-F	**2b**
3	**1c** 4-Cl	**2c**
4	**1d** 4-Br	**2d**
5	**1e** 4-F	**2e**
6	**1f** 4-CH_3	**2f**
7	**1g** 2-CH_3	**2g**
8	**1h** 4-OCH_3	**2h**
9	**1i** 2-OCH_3	**2i**
10	**1j** 4-NO_2	**2j**

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spectra were recorded on Varian Inova-400/500 MHz NMR spectrometer with TMS as an internal reference. IR spectra were recorded as KBr pellets on a Bruker-Tensor 27 spectrometer. HRMS were recorded on an Autoflex tof/tof III mass spectrometer. Silica gel (200–300 mesh) was used to isolate the products.

Synthesis of isopropyl nitrite

Concentrated hydrochloric acid (12.0 mL, 120 mmol) was dropped into the magnetically stirred mixture of sodium nitrite (6.21 g, 90 mmol), isopropanol (13.8 mL, 180 mmol) and water (8.0 mL) at 0–5 °C by means of ice bath. After the addition, this reaction was stirred for 1 h at 0–5 °C. Then isopropyl nitrite, the organic layer, was obtained after separating the aqueous layer.

Synthesis of biphenyl products

The mixture solution of aniline derivatives (30 mmol) and 1,4-methylbezene (40.0 mL) was added dropwise into a mixture of 1,4-dimethylbenzene (20.0 mL), isopropyl nitrite, as prepared above, and CuCl (1.00 g, 10mmol). The reaction was mechanically stirred for 3 h at room temperature. The mixture was filtered to remove CuCl. The solvent was evaporated and the residue purified by column chromatography using PE as the eluent. 2-Fluoro-4-bromobiphenyl was prepared by the same method.

2-Fluoro-4-bromobiphenyl: Yellow solid, 5.65g, 76% (lit.[23] 75%). m.p. 35–36 °C (lit.[23] 36–37 °C). ^{1}H NMR (500 MHz, CD_3OD), δ(ppm): 7.36–7.52(8H, m, ArH_8). ^{13}C NMR (125 MHz, CD_3OD), δ(ppm): 159.63 (d, J = 249.9 Hz, C–F), 134.84, 131.96 (d, J = 4.0 Hz), 128.69 (d, J = 3.0 Hz), 128.45, 127.95, 127.82 (d, J = 3.8 Hz), 121.16 (d, J = 9.5 Hz), 119.48, 119.27.

2,5-Dimethylbiphenyl (**2a**)[24]: Colourless oil, 3.47g, 64% (lit.[25] 78%). ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.17 (3H, 1s, CH_3), 2.31 (3H, 1s, CH_3) and 6.98–7.40 (7H, m, ArH_7). ^{13}C NMR (100 MHz, CD_3OD), δ(ppm): 142.42, 141.95, 135.03, 131.87, 130.11, 130.05, 128.97, 127.92, 127.76, 126.55, 19.88 and 18.98.

2′-Fluoro-2,5-dimethyl-1,1′-biphenyl (**2b**): Colourless oil, 4.41g, 73.4%. IR (KBr^{-1}): 3045, 2923, 1610, 1576, 1504, 1488, 1446, 1254, 1217(C–F), 1103, 810, 762. ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.20 (3H, 1s, CH_3), 2.39 (3H, 1s, CH_3) and 7.08–7.38 (7H, m, ArH_7). ^{13}C NMR (100 MHz, CD_3OD), δ(ppm): 159.70 (d, J = 244.1 Hz, C–F), 135.60, 135.07, 133.51, 131.59 (d, J = 3.7 Hz), 130.74 129.88 128.94(d, J = 7.9 Hz), 128.73, 123.94 (d, J = 3.6 Hz), 115.61, 115.38, 20.91 and 19.43 (d, J = 2.8 Hz). HRMS Calcd for $C_{14}H_{13}F$ 200.1001. Found 200.1006.

4′-Chloro-2,5-dimethyl-1,1′-biphenyl (**2c**):[26] Colourless oil, 4.69g, 72.5% (lit.[26] 95%). ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.24 (3H, 1s, CH_3), 2.37 (3H, 1s, CH_3) and 7.05–7.42 (7H, m, ArH_7). ^{13}C NMR (100 MHz, CD_3OD), δ(ppm): 140.53 (C–Cl), 135.36, 132.74, 132.11, 130.53, 130.39, 128.29, 128.24, 20.91 and 19.90.

4′-Bromo-2,5 -dimethyl-1,1′-biphenyl (**2d**):[27] Orange oil, 5.51g, 70.6% (lit.[28] 26%). ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.18 (3H, 1s, CH_3), 2.32 (3H, 1s, CH_3) and 6.99–7.56 (7H, m, ArH_7). ^{13}C NMR (100 MHz, CD_3OD), δ(ppm): 141.22 (C–Br), 140.36, 135.08, 131.40, 130.85, 130.69, 130.01, 129.72, 127.97, 120.38, 19.62 and 18.69.

4′-Fluoro-2,5-dimethyl-1,1′-biphenyl (**2e**):[29] Yellow oil, 4.43g, 73.7% (lit.[29] 46%). ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.17 (3H, 1s, CH_3), 2.31 (3H, 1s, CH_3) and 6.98–7.29 (7H, m, ArH_7). ^{13}C NMR (100 MHz, CD_3OD), δ(ppm): 161.88 (d, J = 242.6 Hz, C–F), 140.63, 134.95, 131.76, 130.50 (d, J = 7.9 Hz), 129.94 (d, J = 3.2 Hz), 128.55, 128.19, 127.75, 114.48, 114.27, 19.63 and 18.70.

2,4′,5-Trimethyl-1,1′-biphenyl (**2f**):[30] Colourless oil, 3.57g, 60.7% (lit.[30] 24%). ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.14 (3H, 1s, CH_3), 2.28 (3H, 1s, CH_3), 2.35 (3H, 1s, CH_3) and 6.95–7.18 (7H, m, ArH_7). ^{13}C NMR (100 MHz, CD_3OD), δ(ppm): 141.68, 139.24, 135.95, 134.73, 131.71, 129.95, 129.80, 128.65, 128.31, 127.35, 19.85, 19.67 and 18.82.

4′-Methoxy-2,5-dimethyl-1,1′- biphenyl (**2h**)[31]: Colourless oil, 63.7% (lit.[31] 24%). ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.16 (3H, 1s, CH_3), 2.27 (3H, 1s, CH_3), 3.78 (3H, 1s, OCH_3) and 6.90–7.16 (7H, m, ArH_7). ^{13}C NMR (100 MHz, CD_3OD), δ(ppm): 158.60 (C–OCH_3), 141.37, 134.75, 134.49, 131.81, 130.06, 129.83, 127.25, 113.12, 54.30, 19.70 and 18.90.

4′-Nitro-2,5-dimethyl-1,1′-biphenyl (**2j**)[27]: Light yellow solid, 5.16g, 75.8% (lit.[27] 58%). m.p. 83–84 °C (lit.[28] 86–87 °C). ^{1}H NMR (400 MHz, CD_3OD), δ(ppm): 2.23 (3H, 1s, CH_3), 2.34 (3H, 1s, CH_3) and 7.06–8.315 (7H, m, ArH_7). ^{13}C NMR (100 MHz, $CDCl_3$), δ(ppm): 149.04 (C–NO_2), 139.47, 135.67, 131.90, 130.70, 130.09, 129.31, 129.20, 123.48, 123.36, 20.86, and 19.80.

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