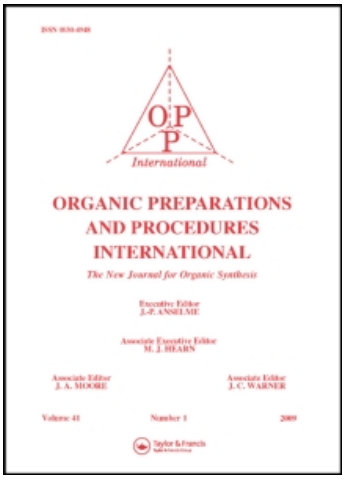

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A Practical Synthesis of 2-Fluoro-4-bromobiphenyl

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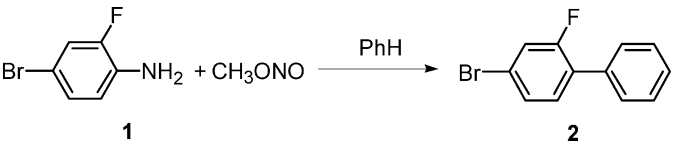
2-Fluoro-4-bromobiphenyl (**2**) is the key intermediate for the manufacture of flurbiprofen,[1,2] a non-steroidal anti-inflammatory and analgesic material. Though compound **2** is a useful molecule, a review of the literature, including patents, indicated the absence of an easily-performed synthesis. Lang *et al*.[3] had developed a cross-coupling reaction of 2-fluoro-4-bromoiodobenzene with phenylboronic acid to obtain 2-fluoro-4-bromobiphenyl in good yield (87%). However, the high cost associated with the use (and removal) of palladium and toxic phenylboronic acid have limited the more widespread use of such protocol in large-scale production. Alternatively, diazotization of 2-fluoro-4-bromoaniline with sodium nitrite and an organic[4] or inorganic acid[5] has commonly been used to generate the diazonium salt for coupling with benzene. However, in spite of all precautions the formation of dark decomposition products is unavoidable thus lowering the yield and making the product difficult to isolate.

As part of our research program on the study of diazotizing systems,[6] we have developed and now report a practical pilot-scale method for the preparation of 2-fluoro-4-bromobiphenyl (*Scheme 1*) from methyl nitrite and 2-fluoro-4-bromoaniline, easily prepared by bromination of 2-fluoroaniline according to the literature procedure.[4] Methyl nitrite is a toxic, volatile, heat-sensitive potentially explosive gas that is not commercially available; its transport is prohibited in the U.S. and the European Union. Therefore its generation previously described by us[6] is reproduced in this article. Proper precautions and a good hood should be used.



1 **2**

Scheme 1

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The above process is efficient, no acid is used[7] during the diazotization, and the reaction mixture is easy to work up because of the use of methyl nitrite.[6] In this reaction, proper control of temperature is important to maintain an adequate reaction rate and satisfactory yield.

Experimental Section

Mps and bps are uncorrected. The purity of products was established on an Agilent 1100 HPLC. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 (400 MHz) instrument with TMS as internal standard. Infrared spectrum was obtained as a KBr pellet on a Shimadzu IR-408 instrument. All chemicals were reagent grade and available commercially. The elemental analysis was performed on a Flash EA1112 instrument.

Methyl Nitrite (prepared just prior to use)

In a 500 mL round-bottomed flask, fitted with a pressure equalizing addition funnel filled with 125 mL 12M hydrochloric acid, and a gas tube in a well ventilated hood, was placed 86.3 g (1.25 mol) of sodium nitrite, 70 mL methanol and 125 mL water. The temperature was raised to 35°C and hydrochloric acid was added dropwise over 1.5 h. The colorless methyl nitrite evolved was passed through a water trap to remove acid and then bubbled through the reaction mixture below *via* the gas tube.

2-Fluoro-4-bromobiphenyl

In a 3 L round-bottomed flask, fitted with a mechanical stirrer, and a gas tube in a well-ventilated hood, was placed 224.0 g (1.18 mol) of 2-fluoro-4-bromoaniline, 15.0 g (0.15 mol) CuCl and 2 L benzene. The temperature was raised to 43°C and methyl nitrite (76.3 g, 1.25 mol, generated as described above) was added through the tube for about 1.5 h while the temperature was kept between 43–47°C by means of water bath. When the reaction was complete, the temperature was raised to 50°C and the mixture was stirred for another 20 min. to expel excess methyl nitrite. The mixture was then cooled to room temperature, washed with 1500 mL water and dried over $MgSO_4$. Benzene was then removed by distillation and recycled. The residue was evaporated under vacuum (105–107°C/0.5 mmHg) to afford 222.0 g (75%) of the product as a white solid, mp. 36–37°C (HPLC >98.5%).

^{1}H NMR (DMSO-d_6): δ 7.31–7.55 (8 H, m). ^{13}C NMR (DMSO-d_6): δ 159.4 (J = 250.4 Hz), 134.7, 131.7 (J = 3.4 Hz), 128.8, 128.7, 128.5, 128.2 (J = 13.1 Hz), 128.0, 127.7, 127.6, 121.2 (J = 9.0 Hz), 119.7 (J = 26.2 Hz). An analytical sample was prepared by recrystallization from benzene and methanol (v/v 5/95), mp. 36.5–37°C, *lit.*[4] mp. 36–37°C.

Anal. Calcd for $C_{12}H_8BrF$: C, 57.40; H, 3.21. Found: C, 57.24; H, 3.13.

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7. When the diazotization was performed with methyl nitrite purified by passing through a water trap and a 10% sodium carbonate trap, the same yield of product was obtained.