A straightforward coupling of 4-sulfonylpyridines with Grignard reagents

Liu-Yi Song¹, Meng-Ke Chen¹, Jian Wang² and Jing-Hua Li¹*²

Abstract

A straightforward synthesis of alkyl-sulfonylpyridines and aryl-sulfonylpyridines is developed by coupling of sulfonylpyridines with the Grignard reagents. The protocol proceeds through a catalyst- and oxidant-free coupling of sulfonylpyridines as substrates via a Chichibabin-type reaction mechanism.

Keywords

alkyl-sulfonylpyridines, aryl-sulfonylpyridines, Chichibabin-type reaction, Grignard reagents

Date received: 9 March 2022; accepted: 11 May 2022

Introduction

Aza-arenes and their derivatives are important naturally occurring substances and building blocks for the synthesis of bioactive compounds with a broad spectrum of activity.¹–³ Transition-metal-catalyzed coupling reactions of 2-halogen-substituted aza-arenes with organometallic reagents provide effective protocols for the construction of 2-alkyl-aza-arenes and 2-aryl-aza-arenes (Scheme 1(a)).⁴–⁷ However, the use of transition metals usually leads to metal residues and environmental pollution. Recent efforts have been directed toward coupling reactions of pyridinium salts with organometallic reagents via a Chichibabin-type reaction mechanism (addition-oxidation), which avoids the use of transition metals (Scheme 1(b)). For example, Knochel and co-workers reported the addition of BF₃-pyridinium salts with magnesium and lithium reagents and subsequent oxidation with chloranil.⁸,⁹ Rappenglück et al. have also described a coupling reaction of N-silylpyridinium salts with organomagnesium reagents,¹⁰ in which an oxidant is necessary in order to obtain aza-arenes. In 1986, Furukawa et al. reported the ipso-substitution reaction of 2- and 4-sulfonylpyridines with several aryl and long-chain alkyl Grignard reagents (Scheme 1(c)).¹¹ Nonetheless, the Chichibabin-type reaction is still not well-developed. Herein, we demonstrate that sulfonylpyridines react with phenyl and short-chain alkyl...
Grignard reagents to generate aryl-sulfonylpyridines and alkyl-sulfonylpyridines via a Chichibabin-type reaction mechanism. The reaction requires neither activation of the pyridine by generating the corresponding pyridinium species nor addition of a catalyst or oxidant (Scheme 1(d)).

**Results and discussion**

Initially, to a mixture of 4-sulfonylpyridine \( 1a \) (1 mmol) in THF was added isopropyl magnesium chloride \( 2a \) (2 mmol) at 0 °C under nitrogen. After 1 h, water was added to quench the reaction, and the desired product \( 3a \) was obtained in 43% yield after work-up (Table 1, entry 2). Encouraged by this result, we further investigated the effect of the catalyst, the solvent, the equivalents of \( 2a \), and the temperature on the reaction yield. Thus, under similar reaction conditions, the amount of \( 2a \) was examined. Reaction with 2.5 equiv. of the Grignard reagent gave a higher yield (Table 1, entries 1–5). Among the reactions performed, that one without a catalyst was better than that with a catalyst (e.g. PdCl\(_2\), NiCl\(_2\), Co(acac)\(_2\), and Fe(acac)\(_3\)). Decreasing or increasing the temperature did not improve the yield (Table 1, entries 6–9). Subsequent investigation of different solvents in this transformation revealed that the solvent played a crucial role, with THF giving the best yield (Table 1, entries 3, and 10–14). Thus, the optimum reaction conditions are as follows: \( 2a \) (2.5 equiv.), no catalyst, anhydrous THF, 0 °C (Table 1, entry 3).

With optimized reaction conditions in hands, we next set out to investigate the substrate scope. The results are summarized in Scheme 2, which show that the method can be applied to various sulfonylpyridines and Grignard reagents to generate the corresponding products \( 3a–w \) in moderate yields. The reactions of aryl-sulfonylpyridines were more productive than those of methylsulfonylpyridine (see \( 3a–f \)). The yields did not differ giving products significantly for different aryl-sulfonylpyridines (see \( 3a, 3g \), and \( 3l \)).

After examining the substrate scope of the reaction with 4-sulfonylpyridines with different Grignard reagents, we next tried replaced the Grignard reagent with a lithium metal reagent. To our surprise, the obtained result was different from the reactions with Grignard reagents. 2,4-Dibutylpyridine was isolated as the main product when 3 equiv. or more of \( n\)-butyllithium were employed (Scheme 3).

**Conclusion**

In summary, we have developed a straightforward synthesis of 2-alkyl-4-sulfonylpyridines and 2-aryl-4-sulfonylpyridines by coupling 4-sulfonylpyridines with various Grignard reagents in the absence of a catalyst or oxidant.

---

**Table 1. Optimization of the reaction conditions.**

| Entry | \( 2a \) (equiv.) | Temp (°C) | Solvent | Yield\(^a\) |
|-------|------------------|----------|---------|------------|
| 1     | 1                | 0        | THF     | 20%        |
| 2     | 2                | 0        | THF     | 43%        |
| 3     | 2.5              | 0        | THF     | 56\(^a\)   |
| 4     | 3                | 0        | THF     | 25%        |
| 5     | 4                | 0        | THF     | 11%        |
| 6     | 2.5              | –78      | THF     | 22%        |
| 7     | 2.5              | –30      | THF     | 31%        |
| 8     | 2.5              | 25       | THF     | 18%        |
| 9     | 2.5              | 66       | THF     | 10%        |
| 10    | 2.5              | 0        | Toluene | 19%        |
| 11    | 2.5              | 0        | Ether   | 37%        |
| 12    | 2.5              | 0        | Isopropyl ether | 15% |
| 13    | 2.5              | 0        | MTBE    | 24%        |
| 14    | 2.5              | 0        | 1,4-dioxane | 12% |

\(^a\)Conditions: anhydrous solvent (2 mL), \( N_2 \).

\(^b\)Yield of isolated product.

\(^c\)No starting material \( 1a \) was detected. Except for the main product \( 3a \), other impurities produced with molecular weight 276.1064, 292.1012, 353.1329, and 364.2316 were detected by LC-HRMS, which might be 3-isopropyl-4-tosylpyridin-1-ium, 1-hydroxy-isopropyl-4-tosylpyridin-1-ium, isopropyl-4-tosyl-[1,4'-bipyridine]-1-ium, and 2,3,6-trisopropyl-4-tosyl-1,2,3,4-tetrahydropyridin-1-ium, respectively.
Experimental

**General**

All sulfonylpyridines were prepared from chloropyridines and sodium sulfite. Other reagents and solvents were purchased from commercial suppliers. Anhydrous solvents were purified and dried following standard procedures. Purification was generally achieved by flash column chromatography on silica gel (200–300 mesh size). Nuclear magnetic resonance (NMR) spectra were recorded on a 500-MHz Bruker spectrometer. Chemical shifts (\(^1\)H and \(^13\)C) are given in ppm relative to the residual solvent peak (CDCl₃, 7.26, 77.0 ppm, respectively). \(^1\)H NMR and \(^13\)C NMR were recorded using tetramethylsilane (TMS) as the internal standard. Spectroscopic data of known compounds matched with the data reported in the corresponding references. All new compounds were further characterized by high-resolution mass spectrometry (HRMS) (EI) (for further details, see the supporting information).

---

**Scheme 2.** Coupling reactions of sulfonylpyridines with Grignard reagents\(^a,b\).

\(^a\)Conditions: sulfonylpyridine (1) (1 mmol), Grignard reagent (2) (2.5 mmol), anhydrous THF (2 mL), \(N_2\), 0 °C, 1 h.

\(^b\)Yield of isolated product.
The reaction mixture was stirred at room temperature. After completion of the reaction, the mixture was poured into saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After removal of the solvent in vacuo, the obtained residue was purified by column chromatography on silica gel to give the desired product.

General procedure A: synthesis of 4-sulfonylpyridines. A round-bottom flask was charged with the: chloropyridine (2 mmol), sodium sulfite (4 mmol), and sodium persulfate (0.4 mmol).¹² Dichloromethane (2 mL) and water (0.8 mL) were added. The reaction mixture was stirred at 0–5 °C for 1 h. After completion of the reaction, the mixture was poured into saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After removal of the solvent in vacuo, the obtained residue was purified by column chromatography on silica gel to give the desired product.

General procedure B: synthesis of 2-alkyl-4-sulfonylpyridines. A three-necked round-bottom flask was charged with the: 4-sulfonylpyridine (1 mmol) and anhydrous THF (2 mL). The air atmosphere was replaced with nitrogen and the reaction mixture was stirred at 0–5 °C for 1 h. After completion of the reaction, the mixture was poured into saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After removal of the solvent in vacuo, the obtained residue was purified by column chromatography on silica gel to give the desired product.

2-Allyl-4-p-toluenesulfonylpyridine (3d): Pale yellow oil; 55% yield; ¹H NMR (500 MHz, CDCl₃): δ 8.70 (d, J = 5.1 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.54 (dd, J = 5.2, 1.7 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 6.08-5.92 (m, 4H), 5.17 (d, J = 11.2 Hz, 2H), 3.64 (d, J = 6.9 Hz, 2H), 2.41 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 162.4, 150.7, 150.6, 145.3, 136.9, 134.3, 130.2, 128.2, 119.4, 118.2, 117.4, 43.8, 36.6, 22.3. HRMS (EI): m/z [M⁺] calcd for C₁₇H₁₅NO₂S: 301.1137; found: 301.1128.

2-Isopropyl-4-methylsulfonylpyridine (3a): Pale yellow oil; 56% yield; ¹H NMR (500 MHz, CDCl₃): δ 8.69 (d, J = 5.1 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 1.0 Hz, 1H), 7.51 (dd, J = 5.1, 1.7 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 3.08-3.18 (m, 1H), 2.42 (s, 3H), 1.30 (d, J = 7.0 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 169.5, 150.5, 150.3, 145.2, 137.0, 130.2, 128.1, 117.9, 117.5, 36.6, 22.3, 21.6. HRMS (EI): m/z [M⁺] calcd for C₁₅H₁₅NO₂S: 275.0980; found: 275.0969.

2-Isopropyl-4-p-toluenesulfonylpyridine (3b): Pale yellow oil; 52% yield; ¹H NMR (500 MHz, CDCl₃): δ 8.69 (d, J = 5.1 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.80 (dd, J = 1.7, 0.8 Hz, 1H), 7.48 (dd, J = 5.1, 1.7 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 2.40 (s, 3H), 1.34 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 171.7, 150.4, 149.9, 144.2, 137.1, 130.2, 128.1, 117.6, 115.7, 38.1, 29.9, 21.6. HRMS (EI): m/z [M⁺] calcd for C₁₆H₁₇NO₂S: 289.1137; found: 289.1150.

2-Cyclohexyl-4-p-toluenesulfonylpyridine (3c): Pale yellow oil; 53% yield; ¹H NMR (500 MHz, CDCl₃): δ 8.66 (d, J = 5.9 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 1.6 Hz, 1H), 7.48 (dd, J = 5.1, 1.8 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 3.26-3.16 (m, 1H), 2.39 (s, 3H), 1.82-1.66 (m, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 168.1, 150.4, 150.2, 145.2, 137.0, 130.2, 128.1, 118.4, 117.4, 43.8, 32.6, 26.3, 25.8, 21.6. HRMS (EI): m/z [M⁺] calcd for C₁₆H₂₁NO₂S: 315.1293; found: 315.1285.

2-Cyclopentyl-4-p-toluenesulfonylpyridine (3e): Pale yellow oil; 55% yield; ¹H NMR (500 MHz, CDCl₃): δ 8.78 (d, J = 5.9 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 1.6 Hz, 1H), 7.48 (dd, J = 5.1, 1.8 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 1.24-1.20 (m, 2H), 1.24-1.20 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 168.1, 150.4, 150.2, 145.2, 137.0, 130.2, 128.1, 118.4, 117.4, 43.8, 32.6, 26.3, 25.8, 21.6. HRMS (EI): m/z [M⁺] calcd for C₁₈H₂₃NO₂S: 315.1295; found: 315.1285.
2-Cyclohexyl-4-p-fluorobenzenesulfonylpyridine (3i): Pale yellow solid; 32% yield; m.p. 136–138 °C (lit. 13); 1H NMR (500 MHz, CDCl 3): δ 8.56 (d, J = 7.1 Hz, 1H), 8.27-8.23 (m, 3H), 7.91 (d, J = 8.4 Hz, 2H), 7.76 (t, J = 8.4 Hz, 1H), 7.51-7.45 (m, 1H), 7.46 (t, J = 8.4 Hz, 2H), 2.38-2.34 (m, 2H), 1.67-1.63 (m, 2H). 13C NMR (126 MHz, CDCl 3): δ 168.2, 167.5, 163.3, 150.4, 149.3, 148.4, 134.4, 130.3, 130.0, 128.0, 127.9, 127.6, 127.5, 127.2, 124.9, 122.5, 32.7, 27.2, 26.9. HRMS (EI): m/z [M]+ calec for C_{19}H_{19}NO_{2}S: 325.1137; found: 325.1139.

2-Cyclohexyl-4-p-toluenesulfonylquinoline (3o): Pale yellow solid; 35% yield; m.p. 212–214 °C (lit. 13); 1H NMR (500 MHz, CDCl 3): δ 8.70 (d, J = 8.6 Hz, 1H), 8.13 (s, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.74-7.69 (m, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 2.22-2.18 (m, 2H), 1.41 (d, J = 6.9 Hz, 3H). 13C NMR (126 MHz, CDCl 3): δ 166.8, 149.2, 145.2, 144.8, 134.8, 131.7, 130.1, 130.0, 128.0, 127.8, 127.6, 124.0, 120.8, 120.3, 48.2, 25.9, 21.6. HRMS (EI): m/z [M]+ calec for C_{22}H_{23}NO_{2}S: 365.1450; found: 365.1436.

2-Phenyl-4-p-toluenesulfonylquinoline (3s): Pale yellow solid; 30% yield; m.p. 163–166 °C (lit. 13); 1H NMR (500 MHz, CDCl 3): δ 8.46 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.70 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 2.22-2.18 (m, 2H), 1.41 (d, J = 6.9 Hz, 3H). 13C NMR (126 MHz, CDCl 3): δ 166.8, 149.2, 145.2, 144.8, 134.8, 131.7, 130.1, 130.0, 128.0, 127.8, 127.6, 124.0, 120.8, 120.3, 48.2, 25.9, 21.6. HRMS (EI): m/z [M]+ calec for C_{19}H_{19}NO_{2}S: 323.0980; found: 323.0981.

2-Phenyl-4-p-toluenesulfonylquinoline (3q): Pale yellow solid; 36% yield; m.p. 171–173 °C (lit. 13); 1H NMR (500 MHz, CDCl 3): δ 8.47 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.73-7.68 (m, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 2.22-2.18 (m, 2H), 1.41 (d, J = 6.9 Hz, 3H). 13C NMR (126 MHz, CDCl 3): δ 166.8, 149.2, 145.2, 144.8, 134.8, 131.7, 130.1, 130.0, 128.0, 127.9, 127.6, 124.0, 120.8, 120.3, 48.2, 25.9, 21.6. HRMS (EI): m/z [M]+ calec for C_{19}H_{19}NO_{2}S: 325.0980; found: 325.0981.

2-Allyl-4-p-toluenesulfonylquinoline (3p): Pale yellow solid; 34% yield; m.p. 170–173 °C (lit. 13); 1H NMR (500 MHz, CDCl 3): δ 8.46 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.70 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 2.22-2.18 (m, 2H), 1.41 (d, J = 6.9 Hz, 3H). 13C NMR (126 MHz, CDCl 3): δ 166.8, 149.2, 145.2, 144.8, 134.8, 131.7, 130.1, 130.0, 128.0, 127.9, 127.6, 124.0, 120.8, 120.3, 48.2, 25.9, 21.6. HRMS (EI): m/z [M]+ calec for C_{19}H_{19}NO_{2}S: 325.0980; found: 325.0981.
2-Benzyl-4-phenylsulfonfyl-7-chloroquinoline (3b): Pale yellow solid; 37% yield; 1H NMR (500 MHz, CDCl3): δ 8.54 (d, J = 9.1 Hz, H1), 8.51 (d, J = 2.2 Hz, H4), 8.09 (s, H7), 8.05 (s, H2, H7), 7.84 (d, J = 8.4 Hz, H2), 7.50 (dd, J = 9.1, 2.2 Hz, H1), 7.30 (d, J = 8.5 Hz, H2), 3.05-3.00 (m, 2H), 2.38 (s, 3H), 1.92-1.83 (m, 2H), 1.03 (t, J = 7.3 Hz, H3). 13C NMR (126 MHz, CDCl3): δ 164.0, 150.8, 145.3, 145.2, 137.2, 136.3, 130.3, 129.0, 128.6, 128.4, 127.8, 125.0, 120.5, 119.2, 47.3, 32.4, 26.3, 25.9, 20.8. HRMS (EI): m/z [M+]+ calcd for C19H18ClNO2S: 359.0747; found: 359.0749.

Declar of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was financially supported by the National Natural Science Foundation of China (no. 22078300) and the Basic Scientific Research Funds of the Department of Education of Zhejiang Providence (no. KYQN202006).

ORCID iD

Jing-Hua Li https://orcid.org/0000-0002-8174-3644

Supplemental material

Supplemental material for this article is available online.

References

1. Roberts RS, Sevilla S, Ferrer M, et al. J Med Chem 2018; 61: 2472.
2. Li Y, Chang Y, Fu J, et al. Eur. J Med Chem 2021; 226: 113845.
3. Gurney ME, Nugent RA, Mo X, et al. J Med Chem 2019; 62: 113845.
4. Sanderson JM, Dominey AP and Percy JM. Angew Chem Int Ed 2017; 56: 4958.
5. Cherney AH, Edelj SJ, Mennen SM, et al. Organometallics 2019; 38: 97.
6. Sengupta D, Basu B, De G, et al. RSC Adv 2014; 4: 35452.
7. Rueping M and lewsuwan W. Synlett 2007; 2: 247.
8. Chen Q, Xavier M and Knochel P. J Am Chem Soc 2013; 135: 4958.
9. Chen Q, Leon T and Knochel P. Angew Chem Int Ed 2014; 53: 8746.
10. Rappenglück S, Niessen K, Seeger T, et al. Synthesis 2017; 49: 4055.
11. Furukawa N, Tsuruoka M and Fujihara H. Heterocycles 1986; 24: 3337.
12. Nguyen VD, Nguyen VT, Haug GC, et al. ACS Catal 2019; 9: 4015.
13. Rodea ND, Arcadia A, Chiarini M, et al. Synthesis 2017; 49: 2501.

General procedure C. synthesis of 2,6-di-n-butylpyridine.

A three-necked round-bottom flask was charged with the: 4-sulfonylpyridine (1 mmol) and anhydrous THF (2 mL). The air atmosphere was replaced with nitrogen and the flask was cooled using liquid nitrogen. When the reaction temperature dropped to −30 °C, n-butyl lithium reagent (3 mmol) was slowly added dropwise to the flask at −30 °C.