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Iron-Catalyzed Synthesis of Cinnarizine

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Abstract—Cinnarizine was synthesized in a high yield by iron-catalyzed cross-coupling of phenylmagnesium chloride with 1-[(2*E*)-3-chloroprop-2-en-1-yl]-4-(diphenylmethyl)piperazine prepared by allylation of 1-(diphenylmethyl)piperazine with (*E*)-1,3-dichloropropene.

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Cinnarizine [**1**, (*E*)-1-(diphenylmethyl)-4-(3-phenylprop-2-en-1-yl)piperazine] is a widely known calcium channel blocker. It acts as vasodilator, enhances cerebral and peripheral circulation, exhibits antihistaminic activity, and reduces vestibular excitability and sympathetic tonus. Cinnarizine is used for the treatment of cerebral atherosclerosis, ischemic stroke, craniocerebral injuries, giddiness, sea sickness, migraine, and other diseases [1–3].

Cinnarizine is commonly synthesized by reactions of 1-(diphenylmethyl)piperazine with cinnamyl chloride and of cinnamylpiperazine with chloro- or bromo(diphenyl)methane [4–6]. Xie et al. [7] recently reported a new version of cinnarizine synthesis via palladium-catalyzed three-component coupling of styrene with paraformaldehyde and 1-(diphenylmethyl)-piperazine. Isomeric (*E*)- and (*Z*)-1-(diphenylmethyl)-4-(3-phenylprop-2-en-1-yl)piperazines (1 : 8) were obtained by the Wittig reaction of 2-[4-(diphenylmethyl)piperazin-1-yl]acetaldehyde with benzyltriphenylphosphonium chloride, followed by chromatographic separation [8].

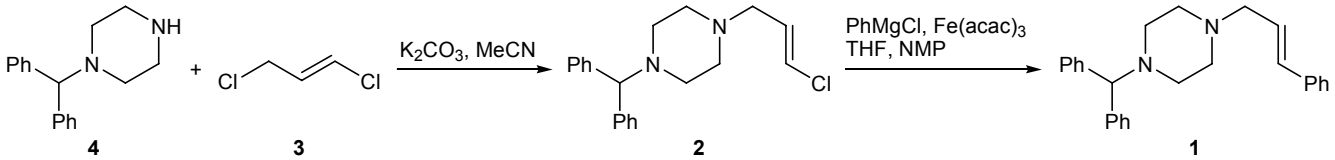
Successful application of various iron-based catalytic systems in the cross-coupling reactions of vinyl halides with Grignard reagents has been reported [9–16]. The goal of the present work was to accomplish stereoselective synthesis of cinnarizine (**1**) by Fe-catalyzed cross coupling of 1-[(2*E*)-3-chloroprop-2-en-1-yl]-4-(diphenylmethyl)piperazine (**2**) with phenylmagnesium chloride (Scheme 1).

Initial stereochemically pure compound **2** was prepared in high yield by nucleophilic substitution of the allylic chlorine atom in (*E*)-1,3-dichloropropene (**3**) by the action of 1-(diphenylmethyl)piperazine (**4**), and the *E* configuration of the double bond was retained [17]. Compound **4** was synthesized in three steps from benzophenone according to the procedure described in [18].

Cross-coupling of compound **2** with 1.8 equiv of phenylmagnesium chloride in the presence of 2 mol % of $Fe(acac)_3$ and 10 mol % of *N*-methylpyrrolidin-2-one (NMP) in THF at room temperature afforded cinnazirine (**1**) with high stereoselectivity (*E*/*Z* ratio 98 : 2) in 90% yield [the *E*/*Z* isomer ratio of initial 1,3-dichloropropene (**3**) was 99 : 1]. The use of excess PhMgCl was necessary to achieve the maximum yield of cinnarizine, otherwise the conversion of **2** was incomplete. Diphenyl formed as by-product in a small amount via homocoupling of phenylmagnesium chloride can be readily removed from compound **1** by column chromatography.

The structure and stereochemical purity of the isolated compounds and configuration of the double bond therein were confirmed by GLC, IR, NMR, and

Scheme 1.



4 **3** **2** **1**

GC/MS data. The *trans* configuration of the double bond in **1** and **2** unambiguously follows from the coupling constants of the vinylic protons (^3J = 15.9, 13.2 Hz) and downfield shift of the allylic carbon signal by ~4–5 ppm relative to the corresponding signal of the *cis* isomer [16, 17]. The most intense peaks in the mass spectra of **1** and **2** belong, respectively, to the cinnamylpiperazine (*m*/*z* 201) and (3-chloroprop-2-en-1-yl)piperazine fragments (*m*/*z* 159) resulting from cleavage of the C–N bond and elimination of diphenylmethyl (*m*/*z* 167).

The proposed procedure for the synthesis of cinnarizine is advantageous due to the use of commercially accessible (*E*)-1,3-dichloropropene (by-product in the manufacture of allyl chloride), as well as due to low toxicity and cost of the iron catalyst.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker AV-500 spectrometer at 500.13 and 125.76 MHz, respectively. The chemical shifts were measured relative to tetramethylsilane (^{1}H) and solvent signal (δ_C 77.00 ppm). The IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer with Fourier transform from samples dispersed in mineral oil or hexachlorobutadiene. Gas chromatographic–mass spectrometric analysis was performed on a Shimadzu GCMS-QP2010S instrument (electron impact, 70 eV; a.m.u. range 33–500; HP-1MS capillary column, 30 m × 0.25 mm, film thickness 0.25 μm; injector temperature 300°C; ion source temperature 200°C; oven temperature programming from 50 to 300°C at a rate of 10 deg/min, followed by 15 min at 300°C; carrier gas helium, flow rate 1.1 mL/min). The high-resolution mass spectra were obtained on a Finnigan MAT 95XP instrument.

1-[(2*E*)-3-Chloroprop-2-en-1-yl]-1-(diphenylmethyl)piperazine (2). 1-(Diphenylmethyl)piperazine (**4**), 2.52 g (0.01 mol), was added to a suspension of 1.22 g (0.011 mol) of (*E*)-1,3-dichloropropene (**3**) and 2.07 g (0.015 mol) of potassium carbonate in 50 mL of anhydrous acetonitrile. The mixture was stirred for 0.5 h at room temperature and was then heated for 4 h under reflux until complete conversion of **4** (GLC). The mixture was cooled and filtered, the precipitate was washed with ethyl acetate, the filtrate was combined with the washings and concentrated, and the residue was purified by column chromatography (SiO_2, hexane–ethyl acetate, 9:1 to 7:3). Yield 2.74 g (84%), colorless crystals, mp 70–71°C. IR spectrum, ν, cm^{-1}: 2808, 2767, 1491, 1450, 1288, 1137, 1009, 947, 760, 706. ^{1}H NMR spectrum, δ, ppm: 2.47 br.s (8H, CH_2N), 2.99 d (2H, C**H**$_2$CH=, J = 7 Hz), 4.22 s (1H, Ph_2C**H**), 5.96 d.t (1H, CH_2C**H**=, J_{trans} = 13.2, 7 Hz), 6.11 d (1H, ClCH=, J_{trans} = 13.2 Hz), 7.15 t (2H, H_{arom}, J = 7.3 Hz), 7.25 t (4H, H_{arom}, J = 7.3 Hz), 7.40 d (4H, H_{arom}, J = 7.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 51.62 (2C, CH_2N), 53.02 (2C, CH_2N), 58.12 (**C**H_2CH=), 76.04 (Ph_2**C**H), 120.55 (ClCH=), 126.86 (2C, CH_{arom}), 127.80 (4C, CH_{arom}), 128.39 (4C, CH_{arom}), 129.92 (CH_2**C**H=), 142.54 (2C, C_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 326 (4) $[M]^+$, 167 (39), 165 (23), 161 (31), 159 (100), 152 (17), 132 (16), 123 (25), 75 (25), 56 (13), 42 (17). Found: *m*/*z* 326.1542 $[M]^+$. $C_{20}H_{23}ClN_2$. Calculated: *M* 326.1550.

(*E*)-1-(Diphenylmethyl)-4-(3-phenylprop-2-en-1-yl)piperazine (1, cinnarizine). A solution of 0.327 g (1 mmol) of compound **2**, 7 mg (0.02 mmol) of $Fe(acac)_3$, and 9.6 μL (0.1 mmol) of *N*-methylpyrrolidin-2-one in 3 mL of THF was cooled to 0°C, 0.9 mL of a 2 M solution of phenylmagnesium chloride in THF was slowly added under argon, and the mixture was stirred for 1 h at room temperature. The mixture was treated with 2 mL of water and 8 mL of ethyl acetate, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×5 mL). The extracts were combined with the organic phase, washed with brine, dried over Na_2SO_4, and concentrated, and the residue was purified by column chromatography (SiO_2, hexane–ethyl acetate, 9:1 to 3:1). Yield 0.331 g (90%), colorless crystals, mp 120–121°C. IR spectrum, ν, cm^{-1}: 2809, 2768, 1492, 1450, 1143, 964, 749, 742, 707, 692. ^{1}H NMR spectrum, δ, ppm: 2.52 br.s (8H, CH_2N), 3.15 d (2H, C**H**$_2$CH=, J = 7 Hz), 4.23 s (1H, Ph_2C**H**), 6.26 d.t (1H, CH_2C**H**=, J_{trans} = 15.9, 7 Hz), 6.49 d (1H, PhC**H**=, J_{trans} = 15.9 Hz), 7.13–7.28 m (9H, H_{arom}), 7.34 d (2H, H_{arom}, J = 7.3 Hz), 7.40 d (4H, H_{arom}, J = 7.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 51.74 (2C, CH_2N), 53.33 (2C, CH_2N), 60.92 (**C**H_2CH=), 76.08 (Ph_2**C**H), 126.21 (2C, CH_{arom}), 126.37 (CH_2**C**H=), 126.80 (2C, CH_{arom}), 127.36 (CH_{arom}), 127.82 (4C, CH_{arom}), 128.36 (4C, CH_{arom}), 128.44 (2C, CH_{arom}), 132.98 (Ph**C**H=), 136.82 (C_{arom}), 142.62 (2C, C_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 368 (1.2) $[M]^+$, 251 (14), 202 (15), 201 (100), 167 (26), 165 (12), 152 (10), 118 (7), 117 (66), 115 (23), 91 (12). Found: *m*/*z* 368.2249 $[M]^+$. $C_{26}H_{28}N_2$. Calculated: *M* 368.2252.

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