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LETTERS TO THE EDITOR

Fe-Catalyzed Synthesis of Flunarizine and Its (*Z*)-Isomer

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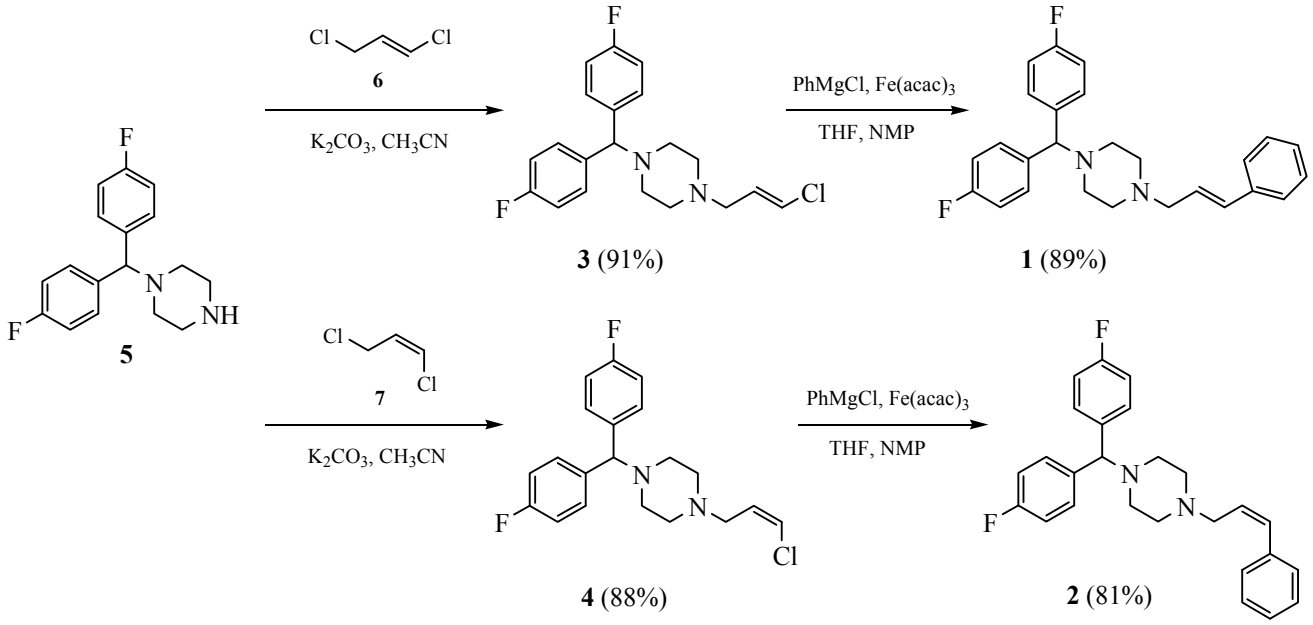
Flunarizine {Sibelium, 1-[bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine} is a well-known drug belonging to calcium channel blockers. It exhibits vasodilating effect, improves cerebral blood circulation, and shows antihistamine activity. Flunarizine is used to treat migraines, dizziness, vestibular disorders, and epilepsy [1–4]. Industrial production of flunarizine is based on condensation of *N*-cynnamylpiperazine with bis(4-fluorophenyl)chloromethane or of cynnamyl chloride with 1-[bis(4-fluorophenyl)-methyl]piperazine [5, 6]. Flunarizine can be obtained by regioselective metal-catalyzed amination of cinnamyl alcohol with 1-[bis(4-fluorophenyl)methyl]piperazine using $Pt(cod)_2Cl_2$–DPEPhos [7] and $Pd(OAc)_2$–1,10-phenanthroline catalysts [8]. (*E*)- and (*Z*)-isomers of 1-[bis(4-fluorophenyl)methyl]-4-(3-phenylprop-2-en-1-yl)piperazine (*E* : *Z* = 1 : 7.4) have been also prepared via Wittig reaction involving {4-[bis(4-fluorophenyl)-methyl]piperazin-1-yl}acetaldehyde and benzyltriphenylphosphonium chloride, followed by isomers separation by column chromatography [9].

Successful application of various Fe-catalyst systems in cross-coupling reactions of vinyl halides with Grignard reagents has been earlier reported in [10–18]. The main advantages of Fe-containing catalysts over conventional platinum group metals are high activity, availability, lower cost, and non-toxicity [19].

Herein, we report stereoselective synthesis of flunarizine **1** and its (*Z*)-isomer **2** based on the Fe-catalyzed cross-coupling of (*E*)- and (Z)-1-[bis(4-fluorophenyl)methyl]-4-(3-chloroprop-2-en-1-yl)piperazines **3** and **4** with phenylmagnesium chloride. Stereochemically pure vinyl chlorides **3** and **4** were prepared via allylation of 1-[bis(4-fluorophenyl)methyl]-piperazine **5** with individual (*E*)- and (*Z*)-isomers of 1,3-dichloropropene **6** and **7**. The peculiarity of 1,3-dichloropropene stereoisomers, a large-scale waste of allyl chloride production, is the prominently different boiling point enabling efficient separation of *trans*- and *cis*-isomers by rectification. Individual stereoisomers of 1,3-dichloropropene containing allyl and vinyl chlorine atoms with different reactivity have unique synthetic potential. A strategy based on the functionalization of 1,3-dichloropropene isomers at the allyl position with *N*-nucleophiles, followed by stereoselective cross-coupling at the vinyl site is very promising for creating stereochemically pure allylamines [20, 21]. Nucleophilic substitution of the allyl chlorine atom afforded compounds **3** and **4** in high yields, while preserving the double bond configuration [22].

Cross-coupling of (*E*)-vinylchloride **3** with 1.8 eq. of phenylmagnesium chloride in the presence of 2 mol % of $Fe(acac)_3$ and 10 mol% of *N*-methylpyrrolidone in THF at room temperature led to the formation of flunarizine **1** in 89% yield. The reaction proceeded with high stereoselectivity, *E* : *Z* = 98 : 2 [isomeric purity of the starting (*E*)-1,3-dichloropropene was 99%]. Use of an excess of PhMgCl was necessary to maximize the yield of flunarizine; the reduction in the reagent load led to incomplete conversion of vinyl chloride **3**. Replacement of PhMgCl with phenylmagnesium bromide resulted in a slight (1–2%) decrease in flunarizine yield. Cross-coupling of (*Z*)-vinyl chloride **4** with PhMgCl under those conditions provided (*Z*)-flunarizine **2** in lower yield (81%) and stereoselectivity (*Z* : *E* = 91 : 9). Side biphenyl was easily separated off the reaction product by column chromatography (Scheme 1).

Scheme 1.



The structure, stereochemical purity, and configuration of the prepared compounds were confirmed by GLC, IR and NMR spectroscopy, and gas chromatography–mass spectrometry data. Reliable proof of the configuration of compounds **1** and **2** was the value of the spin-spin coupling constants of vinyl hydrogen atoms (15.8 and 11.8 Hz, respectively) as well as downfield shifting the signal of flunarizine allyl carbon atom (60.85 ppm) as compared to the same carbon atom of (*Z*)-isomer (55.91 ppm). The strongest signals in the mass spectra of compounds **1**–**4** were assigned to cynnamylpiperazine (*m*/*z* 201) and 3-chloroprop-2-en-1-ylpiperazine (*m*/*z* 159) fragments formed as a result of C–N breaking with elimination of bis(4-fluorophenyl)methyl (*m*/*z* 203).

The advantages of the proposed method of the synthesis of flunarizine and its (*Z*)-isomer are the use of commercially available 1,3-dichloropropene isomers, high yield, mild conditions, and short reaction duration as well as low cost and non-toxicity of Fe-containing catalyst.

1-[Bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-chloroprop-2-en-1-yl]piperazine (3). A mixture of 1.22 g (0.011 mol) of (*E*)-1,3-dichloropropene **6**, 2.07 g (0.015 mol) of K_2CO_3, 50 mL of anhydrous acetonitrile, and 2.88 g (0.01 mol) of 1-[bis(4-fluorophenyl)-methyl]piperazine **5** was stirred for 0.5 h at room temperature, and then for 4 h under reflux until amine **5** was completely consumed (monitoring with GLC). After cooling, the solution was filtered, and the precipitate was washed with ethyl acetate. The combined organic layers were concentrated, and the residue was purified by column chromatography (hexane–ethyl acetate, 9 : 1 → 2 : 1). Yield 3.31 g (91%), colorless crystals, mp 89°C. IR spectrum, ν, cm^{-1}: 1609, 1506, 1453, 1288, 1226, 1153, 1137, 1008, 828. ^1H NMR spectrum, δ, ppm: 2.43 br.s (4H, CH_2N), 2.51 br.s (4H, CH_2N), 3.04 d (2H, C<u>H</u>$_2$CH=, J = 7.0 Hz), 4.23 s (1H, C<u>H</u>Ar_2), 5.98 d.t (1H, CH_2C<u>H</u>=, J_{trans} = 13.2, 7.0 Hz), 6.15 d (1H, ClCH=, J_{trans} = 13.2 Hz), 6.96 t (4H, CH_{Ar}, J = 8.5 Hz), 7.28–7.38 m (4H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 51.51 ($2CH_2N$), 52.97 ($2CH_2N$), 58.10 (C^1), 74.33 (<u>C</u>HAr_2), 115.13 d ($4CH_{Ar}$, $^2J_{CF}$ = 20 Hz), 120.59 (C^3), 129.20 d ($4CH_{Ar}$, $^3J_{CF}$ = 6.8 Hz), 129.96 (C^2), 138.11 ($2C_{Ar}$), 161.78 d ($2CF_{Ar}$, $^1J_{CF}$ = 244.2 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 362 (0.8) $[M]^+$, 203 (41), 201 (19), 183 (30), 161 (31), 159 (100), 132 (13), 123 (32), 75 (34), 56 (15), 42 (22). Mass spectrum (HRMS), *m*/*z*: 362.1348 $[M]^+$ (calculated for $C_{20}H_{21}ClF_2N_2$: 362.1361).

1-[Bis(4-fluorophenyl)methyl]-4-[(2*Z*)-3-chloroprop-2-en-1-yl]piperazine (4) was prepared similarly. Yield 3.19 g (88%). IR spectrum, ν, cm^{-1}: 1603, 1506, 1456, 1296, 1223, 1153, 1135, 1007, 827. ^1H NMR spectrum, δ, ppm: 2.43 br.s (4H, CH_2N), 2.57 br.s (4H, CH_2N), 3.26 d (2H, C<u>H</u>$_2$CH=, J = 7.0 Hz), 4.23 s (1H, C<u>H</u>Ar_2), 5.91 q (1H, CH_2C<u>H</u>=, J = 7.0 Hz), 6.19 d (1H, ClCH=, J_{cis} = 7.0 Hz), 6.96 t (4H, CH_{Ar}, J =

8.6 Hz), 7.28–7.38 m (4H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 51.30 ($2CH_2N$), 53.03 ($2CH_2N$), 54.17 (C^1), 74.24 ($\underline{C}HAr_2$), 115.33 d ($4CH_{Ar}$, $^2J_{CF}$ = 20.1 Hz), 121.13 (C^3), 127.42 (C^2), 129.16 d ($4CH_{Ar}$, $^3J_{CF}$ = 9.0 Hz), 138.02 ($2C_{Ar}$), 161.75 d ($2CF_{Ar}$, $^1J_{CF}$ = 244.2 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 362 (1) $[M]^+$, 203 (42), 201 (17), 183 (26), 161 (32), 159 (100), 132 (17), 123 (22), 75 (24), 56 (18), 42 (19). Mass spectrum (HRMS), *m*/*z*: 362.1350 $[M]^+$ (calculated for $C_{20}H_{21}ClF_2N_2$: 362.1361).

1-[Bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine (flunarizine) (1). A solution of PhMgCl in THF (0.9 mL, 2 mol/L) was added slowly to a solution of 0.363 g (1 mmol) of vinyl chloride **3**, 7 mg (0.02 mmol) of $Fe(acac)_3$, and 9.6 μL (0.1 mmol) of *N*-methylpyrrolidone in 3 mL of THF at 0°C under argon atmosphere. The resulting mixture was stirred at room temperature for 1 h, and then 2 mL of water and 8 mL of ethyl acetate were added to the mixture. The organic layer was separated, and the aqueous layer was treated with ethyl acetate (2 × 5 mL). The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, and concentrated. The reaction product was purified by column chromatography (hexane–ethyl acetate, 9 : 1 → 2 : 1). Yield 0.361 g (89%), colorless crystals, mp 96–99°C. IR spectrum, ν, cm^{-1}: 1601, 1507, 1455, 1377, 1220, 1155, 1138, 1003, 968, 825. ^1H NMR spectrum, δ, ppm: 2.41 br.s (4H, CH_2N), 2.53 br.s (4H, CH_2N), 3.16 d (2H, $C\underline{H}_2CH$=, *J* = 6.8 Hz), 4.23 s (1H, $C\underline{H}Ar_2$), 6.26 d.t (1H, $CH_2C\underline{H}$=, J_{trans} = 15.8, 6.8 Hz), 6.51 d (1H, PhC$\underline{H}$=, J_{trans} = 15.8 Hz), 6.95 t (4H, CH_{Ar}, *J* = 8.7 Hz), 7.16–7.38 m (9H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 51.60 ($2CH_2N$), 53.30 ($2CH_2N$), 60.85 (C^1), 74.36 ($\underline{C}HAr_2$), 115.28 d ($4CH_{Ar}$, $^2J_{CF}$ = 22.6 Hz), 126.25 ($2CH_{Ar}$), 126.34 (C^2), 127.42 (CH_{Ar}), 128.49 ($2CH_{Ar}$), 129.23 d ($4CH_{Ar}$, $^3J_{CF}$ = 6.9 Hz), 133.08 (C^3), 136.88 (C_{Ar}), 138.17 ($2C_{Ar}$), 161.77 d ($2CF_{Ar}$, $^1J_{CF}$ = 246.4 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 404 (3) $[M]^+$, 287 (13), 203 (22), 202 (16), 201 (100), 183 (14), 118 (8), 117 (77), 115 (26), 91 (13), 42 (6). Mass spectrum (HRMS), *m*/*z*: 404.2054 $[M]^+$ (calculated for $C_{26}H_{26}F_2N_2$: 404.2064).

1-[Bis(4-fluorophenyl)methyl]-4-[(2*Z*)-3-phenylprop-2-en-1-yl]piperazine (2) was prepared similarly. Yield 0.327 g (81%). IR spectrum, ν, cm^{-1}: 1603, 1506, 1452, 1297, 1222, 1153, 1136, 1007, 827. ^1H NMR spectrum, δ, ppm: 2.42 br.s (4H, CH_2N), 2.51 br.s (4H, CH_2N), 3.30 d (2H, $C\underline{H}_2CH$=, *J* = 6.6 Hz), 4.21 s (1H, $C\underline{H}Ar_2$), 5.78 d.t (1H, $CH_2C\underline{H}$=, J_{cis} = 11.8, 6.6 Hz), 6.58 d (1H, PhC$\underline{H}$=, J_{cis} = 11.8 Hz), 6.94 t (4H, CH_{Ar}, *J* = 8.6 Hz), 7.21–7.36 m (9H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 51.48 ($2CH_2N$), 53.24 ($2CH_2N$), 55.91 (C^1), 74.30 ($\underline{C}HAr_2$), 115.30 d ($4CH_{Ar}$, $^2J_{CF}$ = 20.3 Hz), 126.85 (CH_{Ar}), 128.08 ($2CH_{Ar}$), 128.79 ($2CH_{Ar,}C^2$), 129.17 d ($4CH_{Ar}$, $^3J_{CF}$ = 6.8 Hz), 131.64 (C^3), 136.91 (C_{Ar}), 138.14 ($2C_{Ar}$), 161.74 d ($2CF_{Ar}$, $^1J_{CF}$ = 244.2 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 404 (1.2) $[M]^+$, 287 (13), 203 (24), 202 (16), 201 (100), 183 (17), 118 (8), 117 (79), 116 (7), 115 (29), 91 (14). Mass spectrum (HRMS), *m*/*z*: 404.2049 $[M]^+$ (calculated for $C_{26}H_{26}F_2N_2$: 404.2064).

^1H and ^{13}C NMR spectra were registered using a AM-300 spectrometer [300.13 (^1H), 75.46 MHz (^{13}C)] in $CDCl_3$. IR spectra were recorded using an IR Prestige-21 Shimadzu FTIR spectrophotometer for the samples in mineral oil and hexachlorobutadiene. GC–MS analysis was performed using a GCMS-QP2010S Shimadzu spectrometer [electron ionization at 70 eV, detected mass range of 33–500 Da, HP-1MS capillary column (30 m × 0.25 mm × 0.25 μm), the evaporator temperature 300°C, ionization chamber temperature 200°C, temperature programming mode from 50 to 300°C at 10 deg min^{-1}, and then at 300°C for 15 min, carrier gas helium (1.1 mL min^{-1})]. Mass spectra were recorded with a MAT 95XP Finnigan high-resolution spectrometer. Column chromatography was performed on 70–230 mesh silica gel (Fluka).

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