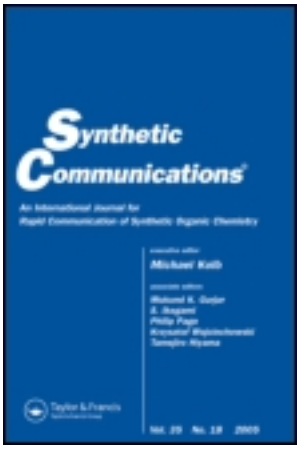

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 03 Jun 2013.

To cite this article: Arava Veerareddy , Gogireddy Surendrareddy & P. K. Dubey (2013): Total Syntheses of AF-2785 and Gamendazole—Experimental Male Oral Contraceptives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:16, 2236-2241

To link to this article: http://dx.doi.org/10.1080/00397911.2012.696306

Synthetic Communications®, 43: 2236–2241, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.696306

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TOTAL SYNTHESES OF AF-2785 AND GAMENDAZOLE—EXPERIMENTAL MALE ORAL CONTRACEPTIVES

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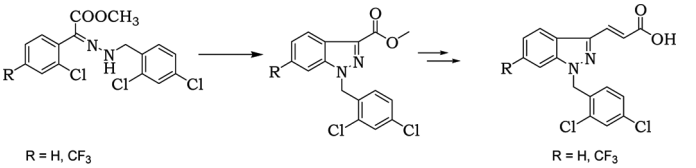
GRAPHICAL ABSTRACT



Abstract *Both AF-2785 and gamendazole are experimental male oral contraceptives. The total syntheses of these two compounds are achieved in good yields.*

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Keywords Buchwald–Hartwig coupling; indazole-3-carboxylic acid; Knoevenagel condensation; male oral contracaptives

INTRODUCTION

Female oral contraceptive drugs are widely available in the market by several trade names, including Altravera, Brevicon, Levora, and i-pill, whereas potentially safer, more convenient, and more effective oral male contraceptives are not yet commercially available. However, there are some experimental drugs.[1–11] AF-2785 **1**, gamendazole **2**, lonidamine **3**, and adjudin **4** are most promising among the experimental Fig. 1, drugs.

AF-2785 and gamendazole fall into the indazole-3-acrylic acid class, and lonidamine and adjudin fall into indazole-3-carboxylic acid class.

George et al.[12] reported the synthesis of gamendazole **2** from 2-chloro-5-trifluoromethyl-1-nitrobenzene in overall yield of 31.5%, whereas Silvestrini and Cheng[13] reported AF-2785 **1** in an overall yield of <20%.

Received April 4, 2012.

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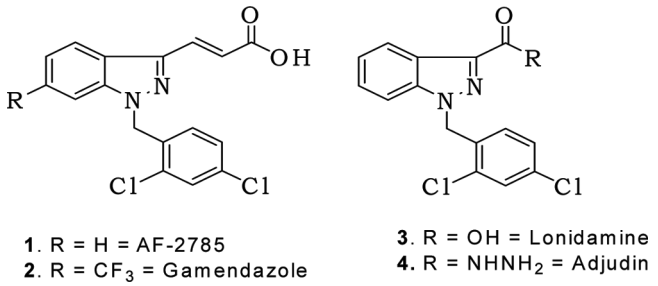


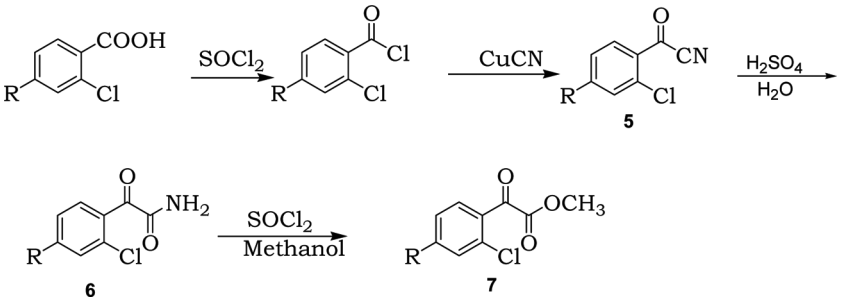
Figure 1. Experimental drugs.

We recently developed[14] a methodology for the synthesis of indazole-3-carboxylic acids from 2-halo benzoic acids via 2-halo-α -ketoacids. As both AF-2785 and gamendazole show very promising results as male antifertility agents, we developed high-yielding syntheses for both of them.

RESULTS AND DISCUSSION

2-Halo benzoic acid is converted into aroyl chloride and then to aroyl cyanide in an overall yield of 82%. Aroyl cyanides **5** are converted to 2-halophenyl glyoxylate ester **7** via ketoamide **6** in 85% yields as shown in Scheme 1. Direct conversion of aroyl cyanide **5** to ester **7** is also reported[15] but with lesser yields.

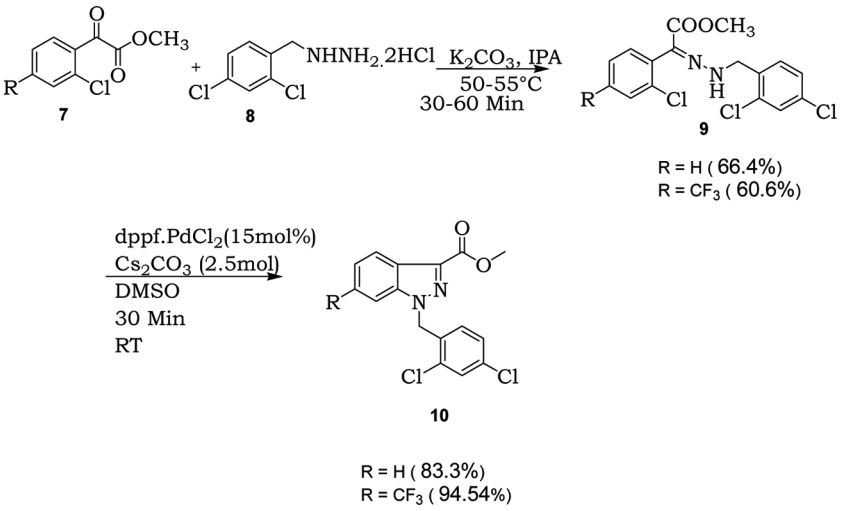
The 2-halophenylglyoxylate **7** esters are reacted with monosubstituted hydrazines **8** to give hydrazones **9**. The monosubstituted hydrazones **9** are cyclized to give indazole esters **10**. This cyclization is best conducted (see Table 1) in the presence of $DPPF \cdot PdCl_2$ in 94.54% yield as shown in Scheme 2.



Scheme 1. Synthesis of 2-halophenylglyoxalate.

Table 1. Conversion of **9** to **10**

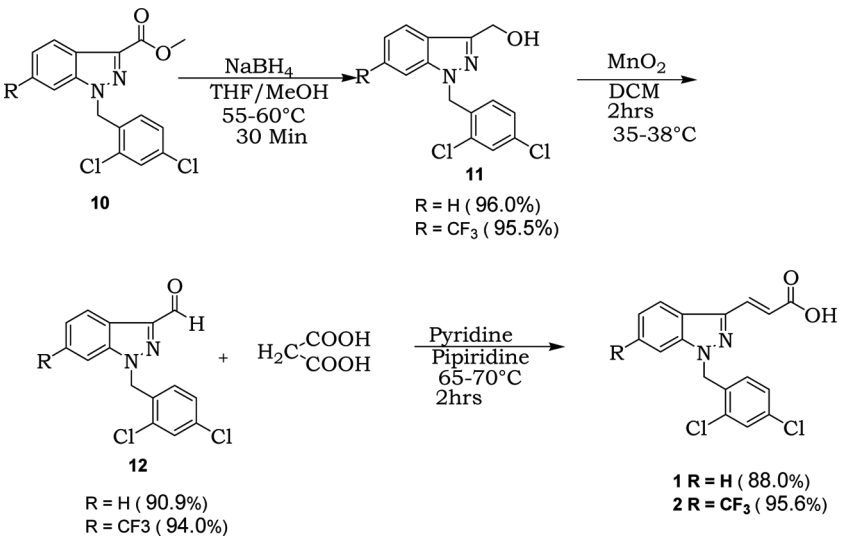
No.	Catalyst/base/solvent	Temp. (°C)	**10** (%) yield
1	CuI/L-Proline/Cs_2CO_3/DMSO	60–65	—
2	CuI/L-Proline/K_2CO_3/DMSO	60–65	—
3	dppf.$Pdcl_2$/Cs_2CO_3/DMSO	25–28	83.3 (R = H)
4	dppf.$Pdcl_2$/Cs_2CO_3/DMSO	25–28	94.5 0 (R = CF_3)



Scheme 2. Synthesis of 1-substituted indazole-3-carboxylate.

The indazole-3-carboxylic esters **10** were reduced with sodium borohydride to alcohol **11** and were oxidized to aldehyde **12** with MnO_2. The aldehyde is converted to acrylic acids with malonic acid (Knoevenagel condensation) to give 88–95.6% yield of the final compounds, as shown in Scheme 3.

In conclusion we have reported a high-yielding syntheses of AF-2785 **1** and gamendazole **2**. The final products **1** and **2** are completely in agreement with the reported[12,13] ones by all spectral means.



Scheme 3. Synthesis of AF-2785 and gamendazole.

EXPERIMENTAL

All reagents were obtained commercially, were of the highest commercial quality, and were used without further purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. Thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC) routinely checked the purity of all compounds. Infrared (IR) spectra were recorded on a Perkin-Elmer model 2000 instrument in KBr phase. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ or dimethyl sulfoxide (DMSO) using a Brucker instrument, and mass spectra were recorded on a Perkin-Elmer mass spectrometer operating at 70 eV.

Preparation of (E)-3-(1-(2,4-Dichlorobenzyl)-1H-indazol-3-yl)acrylic Acid (AF-2785) (1)

1-(2,4-Dichlorobenzyl)-1H-indazole-3-carbaldehyde **12** (R = H) (2.0 g, 0.0065 mol), malonic acid (1.35 g, 0.013 mol), and piperdine (20.0 mg) were added to a solution of pyridine (10.0 ml) at room temperature. The reaction mass was heated to 65 °C and stirred for 2 h. After completion of the reaction, the mass was cooled to rt, and water (50.0 ml) was added and stirred for 30 min at rt. Reaction mass pH was adjusted to 2.0–2.5 with concentrated HCl at 20–25 °C, and ethyl acetate (20.0 ml) was added and stirred for 30 min at rt. Organic layer was separated and washed with brine solution (5.0 ml) at rt. The organic layer was dried over anhydrous Na_2SO_4 and distilled off under vacuum to get the crude compound. To this crude, hexane (5.0 ml) was added, heated to 50 °C, stirred for 30 min, cooled to rt, stirred for 30 min, and filtered to give the solid, which was washed with hexane to get the desired product **1** as a colorless solid (wt 2.0 g, yield 88.0%, HPLC purity 99.56%, DSC: 200.09–201.7 °C). IR (KBr) (cm^{-1}): 3429, 1689, 1629, 1308, 746; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (2H, s), 6.67 (1H, d, $J = 16.24$ Hz), 6.93 (1H, d, $J = 8.36$ Hz), 7.30 (1H, t), 7.35–7.38 (1H, dd, $J_1 = 8.34$ Hz, $J_2 = 2.05$ Hz), 7.47 (1H, t), 7.68 (1H, d, $J = 2.01$), 7.75–7.79 (2H, m), 8.10 (1H, d, $J = 8.19$ Hz), 12.52, (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.73, 110.82, 120.51, 121.10, 122.23, 122.88, 127.54, 128.08, 129.37, 131.18, 133.53, 133.67, 133.73, 135.07, 140.22, 141.43, 167.79. MW for $C_{17}H_{12}Cl_2N_2O_2$: calcd.: 347.1, observed: 347.1 and 349.1 [M + 2]. Anal. calcd. for $C_{17}H_{12}Cl_2N_2O_2$: C, 58.81; H, 3.48; N, 8.07. Found: C, 58.82; H, 3.50; N, 8.10.

Preparation of (E) 3-(1-(2,4-Dichlorobenzyl)-6-(trifluoromethyl)-1H-indazol-3-yl)acrylic Acid (R = CF_3) (Gamendazole) (2)

1-(2,4-Dichlorobenzyl)-6-(trifluoromethyl)-1H-indazole-3-carbaldehyde 12 (R = CF_3) (5.0 g, 0.013 mol), malonic acid (2.78 g, 0.0268 mol), and piperdine (50.0 mg) were added to a solution of pyridine (25.0 ml) at room temperature. The reaction mass was heated to 65 °C and stirred for 2 hrs. After completion of the reaction, the mass was cooled to rt, water (50.0 ml) was added, and it was stirred for 30 min. Reaction mass pH was adjusted to 2.0–2.5 with concentrated HCl at 20–25 °C and extracted with ethyl acetate (100.0 ml). The organic layer was

separated, washed with brine solution (15.0 ml), and dried over anhydrous Na_2SO_4. The organic layer was distilled off under vacuum to get the crude compound. To this crude solid hexane (25.0 ml) was added, heated to 50 °C, and stirred for 30 min at 50–55 °C. It was cooled to rt and stirred for 30 min. The solids were filtered and washed with hexane to get the desired product **2** as a colorless solid (wt 5.32 g, yield 95.6%, HPLC purity 99.30% DSC: 203.4 °C). IR (KBr) (cm^{-1}): 3447, 1697, 1641, 1311, 1122, 872; ^{1}H NMR (400 MHz, DMSO): δ 5.90 (2H, s), 6.72 (1H, d, $J = 16.22$ Hz), 6.94 (1H, d, $J = 8.34$ Hz), 7.36–7.39 (1H, dd, $J_1 = 8.24$ Hz, $J_2 = 1.42$ Hz), 7.55 (1H, d, $J = 8.56$ Hz), 7.69 (1H, d, $J = 1.46$ Hz), 7.78 (1H, d, $J = 16.22$ Hz), 8.37 (1H, d, $J = 8.63$ Hz), 8.40 (1H, s), 12.61 (1H, s); ^{19}F NMR (400 MHz, $CDCl_3$): δ − 59.97(CF_3); ^{13}C NMR (100 MHz, DMSO): δ 50.05, 109.16, 118.73, 121.61, 122.76, 123.39, 123.98, 127.76, 128.11, 129.42, 131.26, 133.56, 133.65, 133.76, 134.10, 140.64, 140.70, 167.57. MW for $C_{18}H_{11}Cl_2F_3N_2O_2$ calcd. 415.19; observed: 415.3 and 417.2. HRMS: calcd.: 415.0228, observed: 415.0225.

ACKNOWLEDGMENT

The authors are grateful to Suven Life Sciences management for allowing them to publish these results.

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