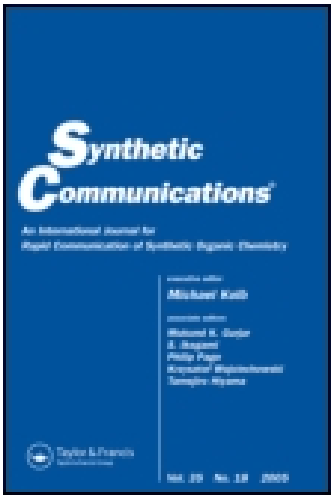

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Concise and Efficient Synthesis of Cinepazide

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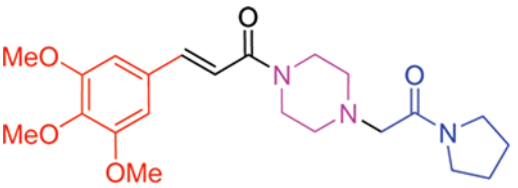
GRAPHICAL ABSTRACT



Abstract *An efficient synthesis of cinepazide has been carried out in four steps with an overall yield of 51%. The synthesis was started from a commercially available 3,4,5-trimethoxy benzaldehyde. All the reactions were very clean and the isolation of products was also very easy.*

Keywords: Amide; coupling; hydrolysis; trimethoxybenzaldehyde; Wittig reaction

INTRODUCTION

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessel, responsible for about 50% of premature deaths in western industrialized countries and 30% of all global deaths.[1] Therefore, extensive research for new and better therapeutic agents continues in different pharmaceutical laboratories, institutions, and universities. The drugs used for CVDs are inotropic, diuretics, vasodilators, angiotensin-converting enzyme inhibitors, and β-blockers. cinepazide has been widely used as a clinical therapeutic drug and it has a vasodilating action by increasing blood flow through the brain and peripheral organs such as cardiac muscle, skeletal muscle, and kidneys.[2]

Cinepazide can inhibit the re-absorption of adenosine and adenosine deaminase activity, delay the adenosine metabolism, and then increase the endogenous adenosine content in local lesions, resulting in the enhancement of the therapeutic effect of adenosine. In addition, cinepazide can inhibit the phosphodiesterase activity,

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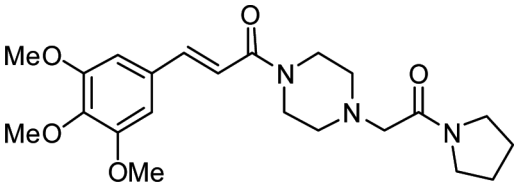


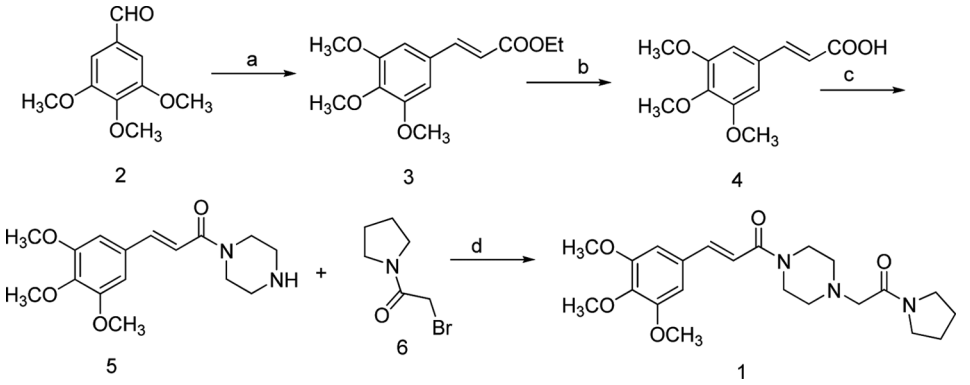
decrease the platelet aggregations, reduce the production of free radicals, decrease the influence of neutrophils on the vascular endothelial cells, and suppress the calcium overload, leading to the decrease of myocardial necrosis, protection of myocardial cells, and improvement of cardiac hemodynamics.[3] Wang and coworkers used mixed anhydride of (*E*)-3,4,5-tri methoxycinnamic acid and pivolyl chloride followed by coupling and alkylation reaction and Othaka et al. used acylation of pyrrolidinocarbonylmethylpiperizine with (*E*)-3,4,5-tri methoxycinnamyl chloride for the synthesis of cinepazide.[4]

The pharmaceutical importance of cinepazide attracted us and as part of our research program in design and synthesis of biologically active compounds[5] we herein report a simple and efficient synthesis for cinepazide.

RESULTS AND DISCUSSION

The synthesis was started from commercially available 3,4,5-trimethoxy benzaldehyde **2**. This aldehyde was subjected to Wittig reaction in benzene to afford (*E*)-ethyl 3-(3,4,5-trimethoxyphenyl)acrylate **3** in 88% yield. The olefin ester compound **3** on hydrolysis with lithium hydroxide in tetrahydrofuran (THF)–H_2O mixture accomplished (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid **4** in 90% yield.

The amide coupling with acrylic acid **4** and piperazine was established in the presence of hydroxy benzotriazole (HOBt) and triethyl amine (TEA) in dichloromethane at low temperature to get (*E*)-1-(piperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one



Scheme 1. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, benzene, rt, 3 h, 88%. (b) LiOH, THF–H_2O (2:1), rt, 5 h, 90%. (c) Piperazine, EDC, HOBT, TEA,CH_2Cl_2, 0 °C, 5 h, 70%. (d) 2-Bromo-1-(pyrrolidin-1-yl)-propan-1-one, acetone, K_2CO_3, PTC, rt, 3 h, 92%.

5 in 70% yield. The amide compound **5** on reaction with 2-bromo-1-(pyrroli din-1-yl)-ethanone **6** in the presence of potassium carbonate (K_2CO_3) in acetone afforded the target molecule, (*E*)-1-{4-[2-oxo-2-(pyrrolidin-1-yl)-ethyl]-piperazin-1-yl}-3-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one **1**, in excellent yields as shown in Scheme 1. All the products were confirmed by their spectroscopic analysis.

CONCLUSION

In conclusion, we have demonstrated a simple and efficient synthetic route for the preparation of cinepazide in four steps with an overall yield in 51%. All the reactions were very clean and the isolation of products is very easy.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 240-c spectro photometer using KBr optics. ^{1}H NMR spectra were recorded on Bruker 300-MHz, spectrometer in $CDCl_3$ using tetramethylesilance(TMS) as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectro meter operating at 70 eV.

(E)-Ethyl-3-(3,4,5-trimethoxyphenyl)acrylate (3)

Ethyl-2-(tritylphosphinyli dene)-acetate (2.12 g, 6.09 mmol) was added to a stirred solution of 3,4,5-tri methoxybenzaldehyde (1 g, 5.1 mmol) in benzene and the resulting reaction mixture was stirred at room temperature. Progress of the reaction was monitored by thin-layer chromatography(TLC), and the reaction was completed within 3 h. Then the reaction mixture was adsorbed on silica gel (60–120 mesh) and eluted with ethyl acetate–hexane mixture (1:9). Pure compound was obtained as colorless liquid, 1.2 g (88.4%). IR (KBr, cm^{-1}): 2974, 2939, 1703, 1633, 1583, 1505, 1455, 1416, 1340, 1314, 1278, 1243, 1182, 1152, 1122, 1036, 990, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, J=7.0 Hz), 3.84 (s, 3H), 3.88 (s, 6H), 4.25 (q, 2H, J=7.0 Hz), 6.29 (d, 1H, J=16 Hz), 6.71 (s, 2H), 7.55 (d, 1H, J=16 Hz); ESI-MS *m/z* (%): 289 ([M+Na]$^+$, 10), 266 (10), 257 (100), 251 (45), 249 (15), 181 (15), 179 (60), 173 (30).

(E)-3-(3,4,5-Trimethoxyphenyl)acrylic Acid (4)

Lithium hydroxide (0.16 g, 6.75 mmol) was added to a stirred solution of (*E*)-ethyl-3-(3,4,5-trimethoxyphenyl)-acrylate (1.2 g, 4.5 mmol) in THF–H_2O (12-6 mL) at 0 °C and continued stirring for 5 h at room temperature. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure, and the residue was diluted by adding cooled water and neutralized with dilute hydrochloric acid. Then the reaction mixture was extracted with ethyl acetate (2×20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh) and eluted with ethyl acetate–hexane mixture (4:6 ratio). Pure compound was obtained as a white

solid, 0.960 g (90%). Mp125–126 °C. IR (KBr, cm^{-1}): 3106, 3004, 2838, 2651, 1670, 1627, 1584, 1505, 1456, 1404, 1332, 1284, 1245, 1121, 994, 828, 729, 616 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 3.81 (*s*, 3H), 3.87 (s, 6H), 6.3 (d, 1H, *J*=15.9 Hz), 6.75 (s, 2H), 7.50 (d, 1H, *J*=15.9 Hz); ESI-MS *m/z* (%): 261 ([M+Na]$^+$, 100), 239 (80), 221 (98), 213 (10), 190 (10), 123 (15), 102 (20).

(E)-1-(Piperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (5)

EDC (0.35 g, 1.82 mmol) was added to a stirred solution of (*E*)-3-(3,4,5-trimethoxyphenyl)-acrylic acid (0.8 g, 3.36 mmol) in dry CH_2Cl_2 (5 mL) followed by HOBt (0.25 g, 1.85 mmol) at room temperature. After 15 min of stirring, the reaction mixture was cooled to 0 °C and a mixture in which piperazine (0.29 g, 3.37 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and then TEA (0.70 mL, 5.04 mmol) were slowly added The resulting reaction mixture was stirred at room temperature for 5 h. The completion of reaction was confirmed by TLC and the reaction mixture was diluted by adding CH_2Cl_2 (10 mL) followed by saturated ammonium chloride solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (2×10 mL) and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh) and eluted with ethyl acetate-hexane mixture (3:7 ratio) to obtain a pure product as yellow syrup, 0.71 g (70%). IR (neat, cm^{-1}): 3429, 2939, 2840, 1644, 1588, 1504, 1458, 1423, 1368, 1337, 1274, 1226, 1126, 1043, 1002, 827, 753, 660 cm^{-1}.; ^1H NMR ($CDCl_3$): δ 2.80-2.95 (m, 4H), 3.50–3.70 (m, 4H), 3.80 (s, 3H), 3.90 (s, 6H), 4.10-4.20 (br s, 1H), 6.60-6.75 (m, 3H), 7.55 (d, 1H, *J*=15 Hz).; ESI-MS *m/z* (%): 329 ([M+Na]$^+$ 20), 307 (100), 221 (75).

(E)-1-{4-[2-Oxo-2-(Pyrrolidin-1-yl)-ethyl]-piperazin-1-yl}-3-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (1)

K_2CO_3 (0.09g, 0.652 mmol) and a catalytic amount of PTC (TBAI) was added to a stirred solution of (*E*)-1-(piperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (0.10 g, 0.326 mmol) in dry acetone (5 mL) After 30 min stirring 2-bromo-1-(pyrrolidin-1-yl)-ethanone (0.074 g, 0.39 mmol), was added which was dissolved in dry acetone (5 mL). The resulting reaction mixture was stirred for 3 h at room temperature and the completion reaction was confirmed by TLC. The solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (2×15 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude product, which was purified by column chromatography using silica gel (60–120 mesh) and eluted with ethyl acetate–hexane mixture (3:7) to obtain a pure product as yellow syrup, 0.124 g (92%). IR (neat, cm^{-1}): 3058, 2925, 1954, 1760, 1701, 1593, 1551, 1515, 1489, 1464, 1442, 1393, 1354, 1252, 1179, 1158, 1077, 1025, 884, 819, 761, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80-2.01 (m, 4H), 2.50-2.70 (m, 4H), 3.13 (s, 2H), 3.35-3.50 (m, 4H), 3.65–3.80 (m, 4H), 3.82 (s, 6H), 3.90 (s, 3H), 6.50-6.75 (m, 3H), 7.52 (d, 1H, *J*=15 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 167.2, 165.3, 153.3, 142.9, 133.2, 122.4, 116,1, 105.3,

104.9, 60.9, 56.2, 56.0, 52.7, 46.1, 45.8, 40.8, 26.1, 24.0; EIMS *m/z* (%): 440 ([M + Na]$^+$, 60), 418 (50), 242 (100), 139 (8).

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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