Stereoselective one-pot synthesis of (*E*)-3-(4-arylpiperazin-1-yl)-1-arylprop-2-en-1-ones

Ai-Jun Li[a]* and Shao-Rui Chen[b]

[a]*College of Chemical and Pharmaceutical Engineering, Hebei University of Science and Technology, Shijiazhuang 050018, P. R. China*

[b]*College of Science, Hebei University of Science and Technology, Shijiazhuang 050018, P. R. China*

A simple and efficient method has been developed for stereoselective one-pot synthesis of (*E*)-3-(4-arylpiperazin-1-yl)-1-arylprop-2-en-1-ones by condensation of aryl ketones with arylpiperazines and N, N-dimethylformamide dimethyl acetal in acetic acid with 54–69% yields. Compared with reported methods, this one-step procedure appears to be a useful approach to prepare (*E*)-β-enaminoketones with good stereoselectivity, simple operation and moderate yields.

Keywords: (*E*)-β-enaminoketones, arylpiperazines, N, N-dimethylformamide dimethyl acetal

The considerable biological activities of β-enaminoketones have attracted a great deal of attention.[1,2] β-Enaminoketones are reported as a class of effective anti-inflammatory agents[3,4] and possess antiviral properties[5] as well. In 2009, Shafiee had reported that β-enaminoketones exhibited dopaminergic activity to some extent.[6] On the other hand, β-enaminoketones are useful intermediates in the synthesis of several heterocyclic systems.[7,8] They can also be used as key starting materials for the stereoselective preparation of 1,3-aminoalcohols,[9] which have pharmacological and biological properties.

Many methods for the synthesis of β-enaminoketones have been developed and reported including: Michael-type reaction of 1-aryl-2-propyn-1-ones with amines,[10,11] condensation of 1,3-diketones with amines,[12–15] amination of α-keto olefins,[16,17] the reaction of β-enaminoesters with organolithium reagents,[18] condensation of amines with β-ketoesters,[19,20] the reaction of imidoylbenzotriazoles with silyl enol ether,[21] reactions of 3-dimethylamino-1-arylprop-2-en-1-ones with various amines[22,23] and the reaction of derivatives of benzoylvinyl alcohols with salts of piperazine.[24,25] These methods have their merits, but all have drawbacks such as harsh reaction conditions, long reaction times, expensive reagents, poor yields or too many by-products.

As an extension of our study on antidepressants, we need a practical and convenient preparative method for (*E*)-3-(4-arylpiperazin-1-yl)-1-arylprop-2-en-1-ones. Herein, we report a concise method for stereoselective synthesis of (*E*)-3-(4-arylpiperazin-1-yl)-1-aryl-prop-2-en-1-ones by a one-pot reaction from aryl ketones **1**. To our knowledge, this method has not been reported in the literature.

In a preliminary experiment, the reaction of 2-acetylthiophene with DMF/DMA and 3-chlorophenylpiperazine was investigated while the reaction progress was monitored by a TLC method. Firstly, we investigated the reaction in solvents such as acetonitrile, toluene, DMF, DMSO, chlorobenzene and acetic acid under the same conditions. When acetic acid was used as solvent, a better yield was obtained. Secondly, the effect of the molar ratios of 2-acetylthiophene to DMF/DMA and 3-chlorophenylpiperazine on the reaction was also examined. When ratio was 1:1.3:1.3, the result was optimal. Finally, various reaction temperatures were screened. When the reaction was achieved at 100 °C, the result was better. Thus, 2-acetylthiophene reacted with DMFDMA (1.3 equiv.) and 3-chlorophenylpiperazine (1.3 equiv.) at 100 °C in acetic acid for 4.5h, then the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate:1/1) to give **2a** in 60% yield.

The structure of **2a** was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS spectra. The identification of the configuration of the enamino double bond in all products was made by comparison of vicinal coupling constants.[10,11] Generally, the *E* isomer has a larger coupling constant than the *Z* isomer. The ^{1}H NMR spectrum of **2a** displays a coupling constant 12.8Hz between the two protons at the enamino double bond that is consistent with the calculated coupling constant deduced from the Karplus equation. As expected, tertiary β-enaminoketones **2a** tend to adopt the *E* configuration due to steric hindrance.

Encouraged by this result, we selected a variety of aryl ketones and arylpiperazines to explore the scope of this reaction under the above optimised conditions. The selected results of this screening process are summarised in Table 1. In all cases, the reaction achieved completion in 6.5h with 54–69% yields and the products mainly adopted the *E* configuration. Compared with reported methods, this procedure appears to be a useful approach to prepare (*E*)-β-enaminoketones with good stereoselectivity, simple operation and moderate yields.

In conclusion, we have investigated a simple procedure for the preparation of (*E*)-3-(4-arylpiperazin-1-yl)-1-arylprop-2-en-1-ones by one-pot reaction from aryl ketones with good stereoselectivity in 54–69% yields. Further study about the effect of various ketones on this reaction is now in progress.

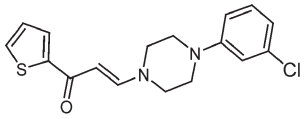
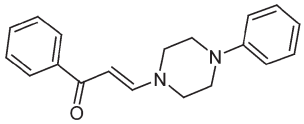
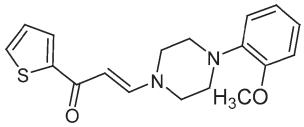
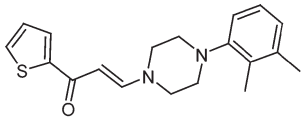
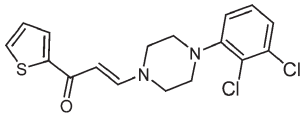
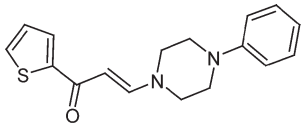
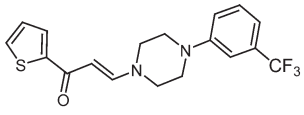
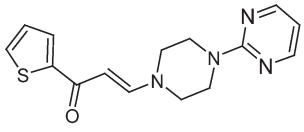
Experimental

All the reagents were obtained commercially and used without further purification. Melting points were measured on an X4 apparatus and were uncorrected. ^{1}H NMR and ^{13}H NMR spectra were recorded in $CDCl_3$ on a Bruker AV400 instrument using tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ (ppm)

Scheme 1

* Correspondent. E-mail: liaj@yeah.net

Table 1 Synthesis of (*E*)-β-3-(arylpiperazinyl)-1-aryl-prop-2-en-1-ones

Entry	Products	Time/h	Yield/%
2a		4.5	60
2b		5.5	58
2c		6	62
2d		4	57
2e		5	69
2f		6	65
2g		7	59
2h		6	54

downfield from TMS, and coupling constants (*J*) are in hertz (Hz). MS were performed on a VGZAB-HS spectrometer (EI at 70eV). HRMS was recorded on a microTOF-QII10204 spectrometer.

*Preparation of **2a–h**; general procedure*

A mixture of aryl ketones (1 mmol), DMF/DMA (0.15 g, 1.3 mmol) and arylpiperazines (1.3 mmol) in acetic acid (10 mL) was stirred at 100 °C for 4–7 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate: 1/1) to give pale yellow products. The physical and spectra data of the compounds **2a–h** are as follows.

(E)-3-(4-(3-Chlorophenylpiperazin-1-yl)-1-(2-thienyl)-prop-2-en-1-one (**2a**): Pale yellow oil, ^{1}H NMR(400MHz, $CDCl_3$): δ 7.78 (d, *J* = 12.8 Hz, 1H, Th-H), 7.65 (m, 1H, Th-H), 7.49(m, 1H, ArH), 7.26–7.18(m, 1H, ArH), 7.10(m, 1H, ArH), 6.89(m, 2H, ArH), 6.80 (d, *J* = 12.8 Hz, 1H, HC=CH), 5.82(d, *J* = 12.8 Hz, 1H, HC=CH), 3.55(t, *J* = 5.6 Hz, 4H, NCH_2), 3.27 (t, *J* = 5.6 Hz, 4H, NCH_2); ^{13}C NMR (400MHz, $CDCl_3$): δ 181.4, 152.0, 151.9, 147.3, 135.3, 130.8, 130.4, 128.9, 127.8, 120.6, 116.8, 114.8, 92.5, 48.9;. EI-MS *m/z*: 331.9, 221.1, 194.1, 166.1, 111.1, 97.1; HRMS(ESI) Calcd for $C_{17}H_{18}ClN_2OS[M+H]^+$: 333.0828. Found 333.0838.

(E)-3-(4-(Phenylpiperazin-1-yl)-1-phenyl-prop-2-en-1-one (**2b**): Pale yellow oil, ^{1}H NMR(400MHz, $CDCl_3$): δ 7.81 (d, *J* = 12.8 Hz, 2H, ArH), 7.54–7.40 (m, 5H, ArH), 7.32–7.26 (m, 2H, ArH), 6.96–6.94(m, 2H, ArH, HC=CH), 5.94 (d, *J* = 12.8 Hz, 1H, HC=CH), 3.57 (t, *J* = 5.4 Hz, 4H, NCH_2), 3.26 (t, *J* = 5.4 Hz, 4H, NCH_2); ^{13}C NMR (400MHz, $CDCl_3$): δ 194.7, 189.1, 152.6, 150.6, 140.2, 138.1, 136.4, 133.9, 133.1, 131.0, 129.2, 128.5, 128.1, 127.4, 120.7, 116.8, 92.4, 49.1; EI-MS *m/z*: 292.2, 173.1, 132.1, 105.1, 77.0; HRMS(ESI) Calcd for $C_{19}H_{21}N_2O[M+H]^+$: 293.1654. Found 293.1671.

(E)-3-(4-(2-Methoxyphenylpiperazin-1-yl)-1-(2-thienyl)-prop-2-en-1-one (**2c**): Pale yellow oil, ^{1}H NMR (400MHz, $CDCl_3$): δ 7.81 (d, *J* = 12.4 Hz, 1H, Th-H), 7.64 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.09 (m, 2H, ArH), 6.95–6.90 (m, 3H, ArH, HC=CH), 5.82 (d, *J* = 12.4 Hz, 1H,HC=CH), 3.90 (s, 3H, OCH_3), 3.60 (m, 4H, NCH_2), 3.15 (m, 4H, NCH_2); ^{13}C NMR (400MHz, $CDCl_3$): δ 181.1, 152.2, 152.1, 147.2, 140.3, 130.2, 128.4, 127.4, 123.7, 121.0, 118.5, 111.4, 91.7, 55.3, 53.2, 50.2; EI-MS *m/z*: 328.1, 190.1, 162.1; HRMS(ESI) Calcd for $C_{18}H_{21}N_2O_2S[M+H]^+$: 329.1234. Found 329.1248.

(E)-3-(4-(2,3-Dimethylphenylpiperazin-1-yl)-1-(2-thienyl)-prop-2-en-1-one (**2d**): Pale yellow oil, ^{1}H NMR (400MHz, $CDCl_3$): δ 7.82 (d, *J* = 12.4 Hz, 1H, Th-H), 7.65 (m, 1H, ArH), 7.50(m, 1H, ArH), 7.10 (m, 2H, ArH), 6.97 (m, 1H, ArH), 6.91(d, *J* = 12.4 Hz, 1H, HC=CH), 5.83 (d, *J* = 12.4 Hz, 1H, HC=CH), 3.56 (m, 4H, NCH_2), 2.97 (m, 4H, NCH_2), 2.29–2.26 (m, 6H, Ar-CH_3); ^{13}C NMR (400MHz, $CDCl_3$): δ 181.1, 152.2, 150.6, 147.2, 138.1, 131.2, 130.3, 128.4, 127.5, 125.9, 125.7, 116.8, 91.7, 53.2, 51.7; EI-MS *m/z*: 326.1, 188.1, 160.1, 105.0; HRMS(ESI) Calcd for $C_{19}H_{23}N_2OS[M+H]^+$: 327.1531. Found 327.1546.

(E)-3-(4-(2,3-Dichlorophenylpiperazin-1-yl)-1-(2-thienyl)-prop-2-en-1-one (**2e**): Pale yellow oil, ^{1}H NMR (400MHz, $CDCl_3$): δ 7.80 (d, *J* = 12.8 Hz, 1H, Th-H), 7.65(m, 1H, ArH), 7.50 (m, 1H, ArH), 7.26–7.20(m, 2H, ArH), 7.09 (m, 1H, ArH), 6.95 (d, *J* = 12.8 Hz, 1H, HC=CH), 5.83 (d, *J* = 12.8 Hz, 1H, HC=CH), 3.60 (m, 4H, NCH_2), 3.13 (m, 4H, NCH_2); ^{13}C NMR (400MHz, $CDCl_3$): δ 181.1, 152.0, 150.2, 147.1, 134.2, 130.4, 128.7, 128.5, 127.7, 127.5, 125.4, 118.7, 92.0, 53.2, 50.8; EI-MS *m/z*: 366.1, 228.1, 200.1, 111.0, 97.0; HRMS(ESI) Calcd for $C_{17}H_{17}Cl_2N_2OS[M+H]^+$: 367.0439. Found 367.0451.

(E)-3-(4-(Phenylpiperazin-1-yl)-1-(2-thienyl)-prop-2-en-1-one (**2f**): Pale yellow oil, ^{1}H NMR (400MHz, $CDCl_3$): δ 7.80 (d, *J* = 12.4 Hz, 1H, Th-H), 7.65 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.32–7.27 (m, 2H, ArH), 7.10 (m, 1H, ArH), 6.92 (m, 3H, ArH, HC=CH), 5.83 (d, *J* = 12.4 Hz, 1H, HC=CH), 3.55 (m, 4H, NCH_2), 3.27 (m, 4H, NCH_2); ^{13}C NMR (400MHz, $CDCl_3$): δ 181.1, 151.8, 150.6, 147.1, 130.4, 129.2, 128.5, 127.5, 120.8, 116.8, 92.0, 53.3, 49.1; EI-MS *m/z*: 298.0, 160.0, 132.1, 104.0; HRMS(ESI) Calcd for $C_{17}H_{19}N_2OS[M+H]^+$: 299.1218. Found 299.1229.

(E)-3-(4-(3-Trifluoromethylphenylpiperazin-1-yl)-1-(2-thienyl)-prop-2-en-1-one (**2g**): Pale yellow oil, ^{1}H NMR (400MHz, $CDCl_3$): δ 7.80 (d, *J* = 12.8 Hz, 1H, Th-H), 7.65 (m, 1H, ArH), 7.51 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.26–7.08 (m, 4H, ArH, HC=CH), 5.84 (d, *J* = 12.8 Hz, 1H, HC=CH), 3.59 (m, 4H, NCH_2), 3.34 (m, 4H, NCH_2). ^{13}C NMR (400MHz, $CDCl_3$): δ 181.1, 151.6, 150.6, 147.0, 131.8, 131.5, 130.6, 129.7, 128.6, 127.5, 125.4, 122.6, 119.4, 117.0, 116.9, 112.9, 92.3, 53.2, 48.6. EI-MS *m/z*: 366.0, 228.1, 200.0, 111.0, 97.0; HRMS(ESI) Calcd for $C_{18}H_{18}F_3N_2OS[M+H]^+$: 367.1092. Found 367.1114.

(E)-3-(4-(2-Pyrimidylphenylpiperazin-1-yl)-1-(2-thienyl)-prop-2-en-1-one (**2h**): Pale yellow oil, ^{1}H NMR (400MHz, $CDCl_3$): δ 8.35 (m, 2H, Pm-H), 7.82 (d, *J* = 12.8 Hz, 1H, Th-H), 7.65 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.10 (m, 2H, ArH, HC=CH), 5.83 (d, *J* = 12.8 Hz, 1H, HC=CH), 3.96 (m, 4H, NCH_2), 3.48 (m, 4H, NCH_2). ^{13}C NMR (400MHz, $CDCl_3$): δ 181.1, 161.3, 157.7, 152.0, 147.1, 130.4, 128.5, 127.5, 127.4, 110.6, 92.0, 53.3, 43.1. EI-MS *m/z*: 300.0, 181.0, 111.0, 98.0; HRMS(ESI) Calcd for $C_{15}H_{17}N_4OS[M+H]^+$: 301.1123. Found 301.1135.

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