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Tracing of ethyl 2-acetyl-3-(arylamino)butanoate intermediates (β-amino ketones) and their structural confinement

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Abstract Tracing of ethyl 2-acetyl-3-(phenylamino)butanoate intermediates (β-amino ketones) was performed during the course of *N*-arylpiperidone synthesis by reaction of aromatic amines, acetaldehyde, and ethyl acetoacetate. The structural confinement and stereochemistry of these molecules were explained by use of 2D NMR spectroscopy and X-ray crystallography.

Keywords Mannich condensation · β-Amino ketones · Ethyl 2-acetyl-3-(phenylamino)butanoates · Intermediates · Piperidin-4-one

Introduction

The stereochemistry and synthesis of 2,6-disubstituted piperidin-4-ones have been of interest since their discovery [1, 2], owing to their biological importance [3, 4]. Prostakov and Gaivoronskaya [5] have reviewed the importance of piperidin-4-ones as intermediates in the synthesis of a variety of physiologically active compounds. Although the synthesis of 2,6-diaryl-substituted piperidin-4-ones has been reported in the literature, we found no report on *N*-arylpiperidin-4-one synthesis by reaction of aromatic amines, acetaldehyde, and ethyl acetoacetate, which is of interest. Most literature methods for piperidin-4-one synthesis do not discuss intermediate formation; the obvious importance of this prompted us to study the formation of intermediates via which differently substituted 4-piperidones can be synthesized.

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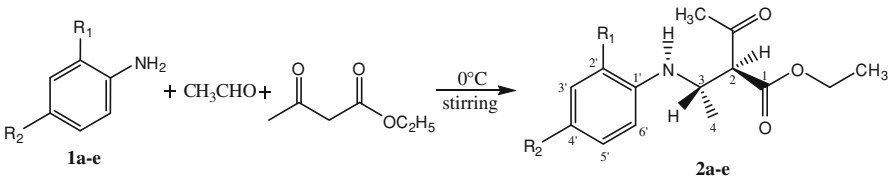
Results and discussion

The three-component reaction of aromatic amines, acetaldehyde, and ethyl acetoacetate does not favor the usual double Mannich condensation for formation of 2,6-disubstituted piperidin-4-ones. It should be noted that the reaction stops at an intermediate stage when conducted at low temperatures (0 °C) using aniline or halo-substituted anilines and ethyl acetoacetate under nitrogen atmosphere, resulting in the formation of ethyl 2-acetyl-3-(phenylamino)butanoates (**2a–e**) (Scheme 1) as crystalline solids [6–8] in high yields (Table 1).

The reaction was expected to proceed via a two-step process. In step 1, nucleophilic addition of an aromatic amine to a carbonyl group followed by dehydration takes place to for the aldimines, whereas in step 2 electrophilic addition of aldimines to the α-methylene carbonyl results in a β-amino carbonyl compound (Mannich base). A plausible mechanism is depicted in Fig. 1, which shows the sequential formation of ethyl 2-acetyl-3-(arylamino)butanoate intermediates.

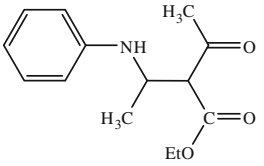
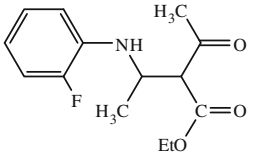
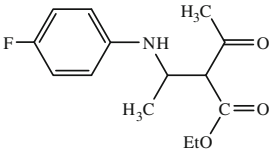
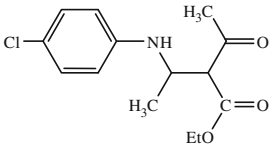
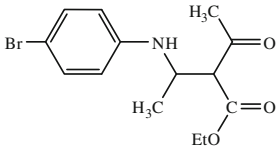
To exclude the possibity of an aldol-type pathway, further reaction between β-amino ketones and the corresponding aldehyde was also attempted, but no reaction was detected (Scheme 2).

In addition, the effect of substituents on the aromatic ring was also investigated. As shown in Table 1, electron-donating groups (halogens) gave better results, and electron-withdrawing groups do not favor formation of the desired intermediate. It is easy to understand that the nucleophilicity of anilino groups was enhanced when electron-donating groups (halogens) were present; this would accelerate the intramolecular substitution to produce the ethyl 2-acetyl-3-(arylamino)butanoates in good yield (Table 1). The structures of the compounds were confirmed by ^{1}H, ^{13}C, and 2D NMR spectroscopy, mass spectrometry, and single-crystal X-ray diffraction studies. From the structures of the products we can see that two stereo centers were generated in one step, which theoretically means that four stereo-isomers would be produced. However, under the reaction conditions used, only one enantiomer with the 2*S*,3*S* configuration was isolated. This might be because of the formation of a carbanion by loss of pro-S hydrogen in the active methylene group of ethyl acetoacetate, which in turn undergoes Si face addition on possible formation of the *E* aldimine leading to the formation ethyl 2*S*-acetyl-3*S*-(arylamino)butanoate. Although the driving force behind the stereoselectivity is unclear, this work assumes importance because different substituted piperidones can be constructed from these intermediates as a base, and they can also act as synthons for construction of a variety of molecules.



Scheme 1 Synthesis of ethyl 2-acetyl-3-(arylamino)butanoates **2a–e**

Table 1 Ethyl 2-acetyl-3-(arylamino)butanoate derivatives

Entry	Aryl amines	Intermediate	Yield (%)
1	$C_6H_5NH_2$		91
2	2F-$C_6H_4NH_2$		88
3	4F-$C_6H_4NH_2$		89
4	4Cl-$C_6H_4NH_2$		90
5	4Br-$C_6H_4NH_2$		88

Experimental

General

Solvents and reagents were commercially sourced and used without further purification. Melting points were taken on Elchem Microprocessor-based DT apparatus in open capillary tubes and are corrected relative to benzoic acid. IR spectra were obtained on an Avatar-330 FTIR spectrophotometer (Thermo Nicolet) using KBr pellets, and only noteworthy absorption levels (reciprocal centimeters) are listed. The NMR spectra were recorded on a Bruker Avance-200 and 300 MHz spectrometer at room temperature using TMS as internal standard (chemical shifts, δ, in ppm). Mass spectra were obtained by use of ESI and GC–MS (Agilent GCMS-5973 Inert MSD series) mass spectrometers. Thin-layer chromatography (TLC) was

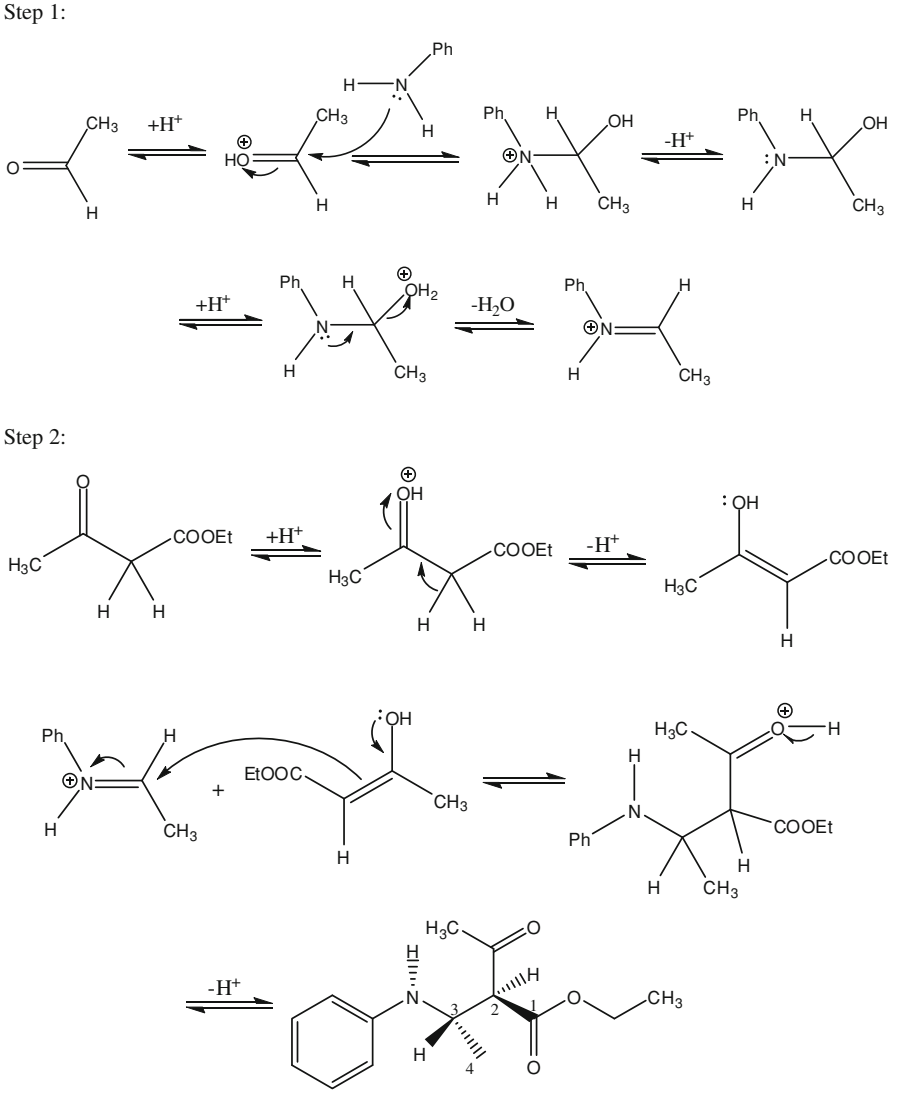
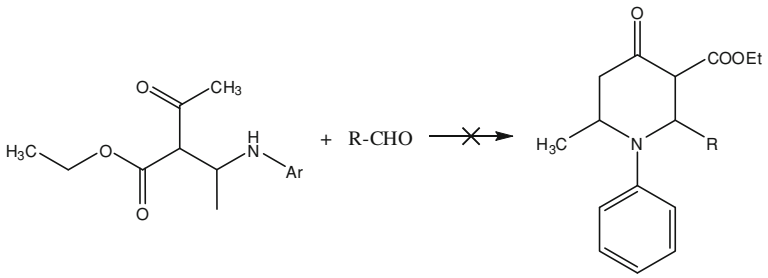


Fig. 1 Plausible mechanism for the formation of ethyl 2-acetyl-3-(arylamino)butanoate intermediates

performed on preparative plates of silica gel (s.d. fine). Visualization was by use of an iodine chamber. Column chromatography was performed on silica gel (60–120 mesh).

General procedure for preparation of ethyl 2-acetyl-3-anilinobutanoate derivatives (2a–e)

A mixture of aniline or substituted aniline (1 mol) and acetaldehyde (2 mol) was placed in a round-bottomed flask containing ethanol (20 mL) and stirred at 0 °C for



Scheme 2 Reaction of β-amino ketones with aldehydes (aldol-type pathway)

30 min. Ethyl acetoacetate (1 mol) in 10 mL ethanol was then added dropwise with stirring. The reaction mixture was then stirred for a further 5 h under a nitrogen atmosphere at 0 °C. Progress of the reaction was monitored by TLC. A paste-like solid was formed, which was repeatedly washed with diethyl ether. The resulting compound was recrystallized from diethyl ether, affording the products **2a–e** in the pure form.

Ethyl 2-acetyl-3-anilinobutanoate **(2a)**

White crystalline solid; m.p: 90 °C (diethyl ether). IR spectrum, v, cm^{-1}: 3327 (NH), 2972, 1728 (CO), 1701 (COOEt), 1602, 1293; ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.25–1.28 (m, 6H, –C$\underline{H}_3$CH, –CH$_2$C$\underline{H}_3$); 2.24 (s, 3H, –C$\underline{H}_3$CO); 3.64 (d, 1H, $J = 6.9$, –COC$\underline{H}$CO); 3.84 (bs, 1H, –N$\underline{H}$); 4.15–4.25 (m, 3H, –OC$\underline{H}_2$CH$_3$, –NHC$\underline{H}$); 6.65–6.70 (m, 3H, H-4′, 2′, 6′); 7.17 (t, 2H, $J = 7.95$, H-3′, 5′); ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (J, Hz): 14.08 (–CH$_2$C$\underline{H}_3$); 18.59 (–CHC$\underline{H}_3$); 29.45 (–C$\underline{H}_3$CO); 48.87 (–NHC$\underline{H}$CH); 61.51 (–C$\underline{H}_2$CH$_3$); 63.97 (–COC$\underline{H}$); 114.01 (C-2′, 6′); 118.28 (C-4′), 129.40 (C-3′, 5′); 146.44 (C-1′); 168.36 (–C$\underline{O}$OCH$_3$); 202.99 (–CH$_3$C$\underline{O}$); GC–MS (m/z): 249 [M$^+$]; Anal Calcd for $C_{14}H_{19}NO_3$: C 67.45, H 7.68, N 5.62; Found: C 67.72, H 7.75, N 5.59.

Ethyl 2-acetyl-3-(2-fluorophenylamino)butanoate **(2b)**

White crystalline solid; m.p: 86 °C (diethyl ether). IR spectrum, v, cm^{-1}: 3358 (–NH), 2980, 1736 (–CO), 1700 (–COOEt); ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.25–1.29 (m, 6H, –C$\underline{H}_3$CH, –CH$_2$C$\underline{H}_3$); 2.26 (s, 3H, –C$\underline{H}_3$CO); 3.67 (d, 1H, $J = 6.5$, –COC$\underline{H}$CO); 4.11 (bs, 1H, –N$\underline{H}$); 4.16–4.25 (m, 3H, –OC$\underline{H}_2$CH$_3$, –NHC$\underline{H}$); 6.53–6.68 (q, 1H, H-4′); 6.78 (t, 1H, $J = 9$, H-3′); 6.93–7.02 (m, 2H, H-5′, 6′); ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (J, Hz): 14.05 (–CH$_2$C$\underline{H}_3$); 18.69 (–CHC$\underline{H}_3$); 29.82 (–C$\underline{H}_3$CO); 48.66 (–NHC$\underline{H}$CH); 61.60 (–C$\underline{H}_2$CH$_3$); 63.77 (–COC$\underline{H}$CH); 113.37 (C-6′); 114.85 (C-3′, $J^2_{C-F} = 18.75$), 117.66 (C-4′, $J^3_{C-F} = 6.75$); 124.67 (C-5′, $J^4_{C-F} = 3$); 134.91 (C-1′, $J^2_{C-F} = 11.25$); 152.04 (C-2′, $J^1_{C-F} = 237$); 168.20 (–C$\underline{O}$OCH$_3$); 202.90 (–CH$_3$C$\underline{O}$); ESI (m/z): 268.1 [M+1]; Anal Calcd for $C_{14}H_{18}FNO_3$: C 62.91, H 6.79, N 5.24; Found: C 62.85, H 6.86, N 5.22.

Ethyl 2-acetyl-3-(4-fluorophenylamino)butanoate **(2c)**

White crystalline solid; m.p: 74 °C (diethyl ether). IR spectrum, v, cm^{-1}: 3316 (–NH), 2979, 1733 (–CO), 1703 (–COOEt), 1508; ^1H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.24–1.31 (m, 6H, $-C\underline{H}_3CH$, $-CH_2C\underline{H}_3$); 2.27 (s, 3H, $-C\underline{H}_3CO$); 3.67 (d, 1H, $J = 6$, $-COC\underline{H}CO$); 4.06 (bs, 1H, –NH); 4.15–4.27 (m, 3H, $-OC\underline{H}_2CH_3$, $-NHC\underline{H}$); 6.61–6.68 (m, 2H, H-2′, 6′); 6.93–7.02 (m, 2H, H-3′, 5′); ESI(m/z): 268.1 [M+1]. Anal Calcd for $C_{14}H_{18}FNO_3$: C 62.91, H 6.79, N 5.24; Found: C 63.24, H 6.86, N 5.19.

Ethyl 2-acetyl-3-(4-chlorophenylamino)butanoate **(2d)**

White crystalline solid; m.p: 84 °C (diethyl ether). IR spectrum, v, cm^{-1}: 3338 (–NH), 2982, 1726 (–CO), 1703 (–COOEt), 1598, 1294; ^1H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.22–1.29 (m, 6H, $-C\underline{H}_3CH$, $-CH_2C\underline{H}_3$); 2.25 (s, 3H, $-C\underline{H}_3CO$); 3.62 (d, 1H, $J = 6$, $-COC\underline{H}CO$); 3.96 (bs, 1H, –NH); 4.14–4.24 (m, 3H, $-OC\underline{H}_2CH_3$, $-NHC\underline{H}$); 6.56 (d, 2H, $J = 8$, H-2′, 6′); 7.12 (d, 2H, $J = 10$, H-3′, 5′); ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (J, Hz): 14.03 ($-CH_2\underline{C}H_3$); 18.46 ($-CH\underline{C}H_3$); 29.74 ($-\underline{C}H_3CO$); 49.07 ($-NH\underline{C}H$); 61.58 ($-\underline{C}H_2CH_3$); 63.48 ($-CO\underline{C}H$); 114.99 (C-2′, 6′); 122.71 (C-4′), 129.17 (C-3′, 5′); 145.04 (C-1′); 168.19 ($-\underline{C}OOCH_3$); 202.94 ($-CH_3\underline{C}O$); ESI (m/z): 284.1 [M+1]. Anal Calcd for $C_{14}H_{18}ClNO_3$: C 59.26, H 6.39, N 4.94; Found: C 59.43, H 6.41, N 4.91.

Ethyl 2-acetyl-3-(4-bromophenylamino)butanoate **(2e)**

White crystalline solid; m.p: 76 °C (diethyl ether). IR spectrum, v, cm^{-1}: 3337 (–NH), 2981, 1725 (–CO), 1701 (–COOEt), 1595, 1294; ^1H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.24–1.28 (m, 6H, $-C\underline{H}_3CH$, $-CH_2C\underline{H}_3$); 2.26 (s, 3H, $-C\underline{H}_3CO$); 3.62 (d, 1H, $J = 6$, $-COC\underline{H}CO$); 3.82 (bs, 1H, –NH); 4.17–4.26 (m, 3H, $-OC\underline{H}_2CH_3$, $-NHC\underline{H}$); 6.62 (d, 2H, $J = 8$, H-2′, 6′); 7.19 (d, 2H, $J = 8$, H-3′, 5′); ESI (m/z): 328.0 [M+1]. Anal Calcd for $C_{14}H_{18}BrNO_3$: C 51.23, H 5.53, N 4.27; Found: C 51.12, H 5.56, N 4.33.

Conclusion

We have described the synthesis of novel ethyl 2-acetyl-3-(arylamino)butanoates as intermediates in piperidin-4-one synthesis. The stereochemistry, and the configuration at the stereo centers, is also described. A plausible mechanism is given to explain formation of product. This method results in clean conversion and high selectivity, and workup is easy, making this procedure practical and economically attractive.

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