Regioselective acylation of β-enaminones of homoveratrylamine

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Abstract
The selective acylation of the aromatic ring of *N*-phenethyl enaminones is reported. A number of substituents in the β-enaminone structure and in the benzene ring have been prepared from different dicarbonyl compounds and carboxylic acids.

Keywords: Enaminones, regioselective acylation, dicarbonyl compounds, homoveratrylamine

Introduction

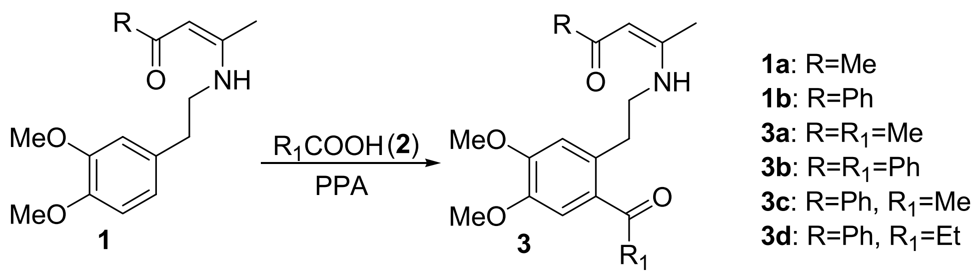
The various reactivities associated with the conjugated system N-C=C-C=O make the β-enaminones valuable reagents with promising applications in heterocyclic synthesis. The versatility of β-enaminones as synthetic intermediates has drawn considerable attention to this class of compounds.[1,2] Their synthetic applications have been extensively reviewed.[3,4] Functionalized 1,2,3,4-tetrahydro-β-carbolines[5] and 1,2,3,4-tetrahydroisoquinolines[6,7] can be synthesized via the Pictet-Spengler reaction starting from β-enaminones containing (hetero)arylethyl substituents tethered to the nitrogen. Some β-enaminones are pharmacologically active in their own right and exhibit anticonvulsant activity.[8-11] It has been shown that these compounds exert their anticonvulsant properties in the µM range by binding to the voltage-dependent sodium channel.

Result and Discussion

We investigated the acylation of some β-enaminones containing activated benzene ring under conditions normally used for Friedel-Crafts-type acylations. The Friedel-Crafts acylation of activated benzene rings in the presence of polyphosphoric acid (PPA) is a very convenient method for direct synthesis of aromatic ketones.[12-14] In our previous reports we have shown that the reaction of homoveratrylamine with carboxylic acids, their esters or anhydrides in PPA affords the corresponding 3,4-dihydroisoquinolines in very good yields and purity.[15] This reaction was also applied to preparation of 1-substituted 3,4-dihydro-β-carbolines[16] and quinazolinones.[17]

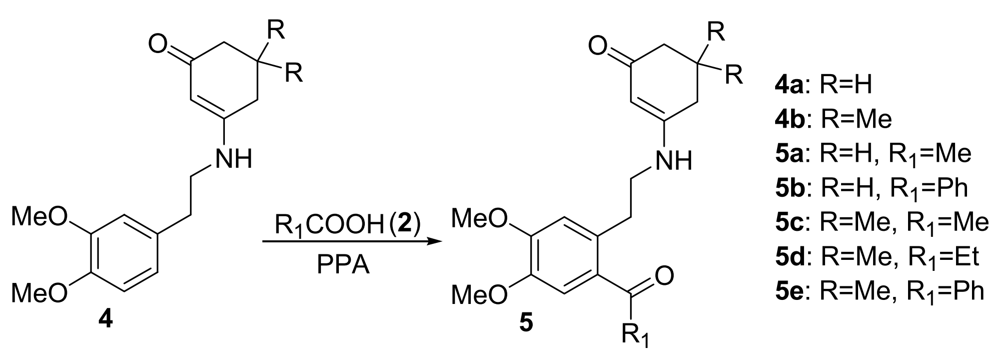
Since the interest of β-enaminones keeps growing, we investigated the acylation regioselectivity of some of them. The starting β-enaminones **1** were obtained by condensation of 2-(3,4-dimethoxyphenyl)ethylamine (homoveratrylamine) with acetylacetone, benzoylacetone, 1,3-cyclohexanedione and 5,5-dimethyl-cyclohexanedione (dimedone) according to a literature procedure.[18] Enaminones of cyclic diketones were obtained by refluxing for 3 h in dichloroethane. Homoveratrylamine was chosen for these studies because it is a widely used compound for the synthesis of various isoquinolines.

The regioselectivity of the acylation depends on the enaminone structure, reactivity of the reagents and reaction conditions.[7,19-24] The results obtained reveal that when the acylation of β-enaminones with carboxylic acid in PPA is carried out at 80°C for 2 h the corresponding acylated products in low yield are obtained. The reaction also gave corresponding 3,4-dihydroisoquinoline. We obtained the acylated products with higher yields and purity, when the mixture was stirred continuously at room temperature for 7 days (Scheme 1).



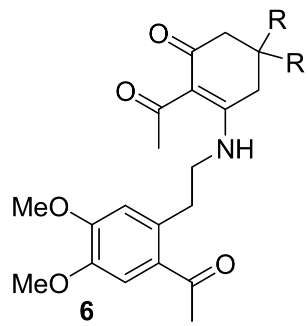
Scheme 1

We found that starting from β-enaminones of cyclic dicarbonyl compounds **4**, as cyclohexanedione or dimedone, the reaction proceeded at 80°C for 3h and gave product **5** with high yields (50-80 %) (Scheme 2).



Scheme 2

It also established that acylation of enaminone of cyclic diketones with acetic acid resulted in formation of two products – major **5** (acylated in the benzene ring) and minor **6** (either acylated in benzene ring and C-acylated) product.



6a: R=H
6b: R=Me

Scheme 3

In conclusion, we succeeded in acylation selectively the aromatic ring of N-phenethyl enaminones **1** and **4**, keeping the enaminone moiety intact. A number of substituents in the β-enaminone structure and in the benzene ring can be varied by using different dicarbonyl compounds and carboxylic acids.

Experimental Section

General Procedures. Melting points were determined on a Boetius hostage apparatus and are uncorrected. 1H-NMR and 13C-NMR were measured in Bruker-250 devise by using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) were referenced to TMS (δ=0.00ppm) as an internal standard and coupling constants are indicated in Hz. Unless otherwise noted, all the NMR spectra were taken at rt (ac. 295 K). MS were recorded on a Jeol JMS-D300 spectrometer (70 eV). All new compounds had correct parent ion peaks by mass spectrometry. Elemental analyses were performed in the analytical laboratory at the Faculty of Chemistry, University of Plovdiv.

Preparation of β-enaminones 1a,b;4a,b.[18] Homoveratrylamine (10 mmol) was added to a solution of the corresponding 1,3-dicarbonyl compound (10 mmol) in 20 ml dichloromethane (dichloroethane for **4 a,b**). The reaction mixture was stirred overnight at rt (3 h reflux for **4 a,b**). After completion of the reaction the solvent removed by disillation. Enaminones crystallized directly from the reaction mixture.

4-[2-(3,4-Dimethoxyphenyl)-ethylamino]-pent-3-en-2-one (1a). Known compound, 98 % yield, mp 37-40ºC.[18]

3-[2-(3,4-Dimethoxyphenyl)-ethylamino]-1-phenyl-but-2-en-1-one (1b). Known compound, 98 % yield, mp 81-83ºC.[18]

3-[2-(3,4-Dimethoxyphenyl)-ethylamino]-cyclohex-2-enone (4a). Yield 90%, mp 110-114°C; ^{1}H-NMR: 1.87-1.94(m, 2H), 2.28(t, 4H, J=3.6), 3.02(t, 2H, J=6.5), 3.34(q, 2H, J=6.5), 3.91(s, 3H), 3.93(s, 3H), 5.09(s, 1H), 5.21(s,1H,NH), 7.05-7.15(m, 3H). MS m/z: 275 (M+); Anal. calcd. for $C_{16}H_{21}NO_3$: C 69.79, H 7.69, N 5.09. Found: C 69.91, H 7.81, N 5.21.

3-[2-(3,4-Dimethoxyphenyl)-ethylamino]-5,5-dimethyl-cyclohex-2-enone (4b). Yield 90%, mp 161-166°C, ^{1}H-NMR: 1.06 (s, 6H), 2.16(s, 4H), 2.85(t, 2H, J=7), 3.34(q, 2H, J=7), 3.86(s, 6H), 5.17(s, 1H), 5.29(s, 1H,NH), 6.70-6.83(m, 3H). MS m/z: 303 (M+); Anal. calcd. for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62. Found: C 71.39, H 8.43, N 4.74.

Acylation of enaminones. General procedure

To a solution of corresponding enaminone of homoveratrylamine **1 or 4** (5 mmol) and the corresponding carboxylic acid **2** (7 mmol) in dichloromethane (10 mL) is added PPA (7g). The reaction mixture is stirred for 2 h at 80°C for enaminones of cyclic diketones (or overnight at rt for others), then poured on crushed ice. The solution was carefully alkalized with 25 % ammonia, then extracted with CH_2Cl_2 (3x20 ml) and combined extracts were dried (Na_2SO_4) and filtered on short column with silica gel. The products, after evaporation of the solvent, were purified by column chromatography on silica gel using n-hexane:Et_2O =1:1 or Et_2O as eluent.

4-[2-(2-Acetyl-4,5-dimethoxyphenyl)ethylamino]-pent-3-en-2-one (3a). Yield 80%, mp 129-131°C, ^{1}H-NMR: 1.70(s, 3H), 1.93(s, 3H), 2.53(s, 3H), 3.03(t, 2H,J=7), 3.52(q, 2H, J=6.6), 3.88(s, 6H), 4.84(s, 1H), 6.70(s, 1H), 7.22(s, 1H), 10.93(s, 1H,NH); ^{13}C-NMR: 199.3 (Ar-*C*=O), 194.3 (N-C=C-*C*=O), 163.4 (NH-*C*=C), 151.6, 146.8, 134.1, 128.9, 120.7, 115.2, 113.4, 95.0 (NH-C=*C*), 56.0, 55.9, 44.3, 35.8, 29.1, 28.6, 18.5. MS m/z: 305 (M+); Anal. calcd. for $C_{17}H_{23}NO_4$: C 66.86, H 7.59, N 4.59. Found: C 66.98, H 7.71, N 4.72.

3-[2-(2-Benzoyl-4,5-dimethoxyphenyl)ethylamino]-1-phenyl-but-2-en-1-one (3b). Yield 78%, oil, ^{1}H-NMR: 1.86(s, 3H), 2.89(t, 2H,J=7), 3.56(q, 2H, J=6.6), 3.79(s, 3H), 3.91(s, 3H), 5.30(s, 1H), 6.82(s, 1H), 6.87(s, 1H), 7.29-7.63(m, 4H), 7.80-7.89(m, 6H), 11.66(s, 1H,NH); ^{13}C-NMR: 197.3 (Ar-*C*=O), 187.4 (N-C=C-*C*=O), 165.4 (NH-*C*=C), 150.9, 146.6, 140.5, 138.4, 132.9, 130.2, 128.1, 126.8, 114.6, 113.4, 112.4, 111.5, 92.1 (NH-C=*C*), 56.1, 55.9, 45.3, 36.6, 34.9, 19.3. MS m/z: 429 (M+); Anal. calcd. for $C_{27}H_{27}NO_4$: C 75.50, H 6.34, N 3.26. Found: C 75.64, H 6.45, N 3.39.

3-[2-(2-Acetyl-4,5-dimethoxyphenyl)ethylamino]-1-phenyl-but-2-en-1-one (3c). Yield 78%, mp 73-75°C, ^{1}H-NMR: 1.86(s, 3H), 2.59(s, 3H), 3.11(q, 2H, J=6.5), 3.64(q, 2H, J=6.5), 3.88(s, 3H), 3.91(s, 3H), 5.57(s, 1H), 6.78(s, 1H), 7.26(s, 1H), 7.32-7.48(m, 4H), 7.79-7.88(m, 2H), 11.61(s, 1H,NH); ^{13}C-NMR: 199.4 (Ar-*C*=O), 187.2 (N-C=C-*C*=O), 165.4 (NH-*C*=C), 151.7, 146.8, 140.4, 133.9, 130.3, 128.9, 128.1, 126.7, 115.3, 113.4, 91.8 (NH-C=*C*), 56.1, 55.9, 44.6, 35.8, 29.2, 19.1. MS m/z: 367 (M+); Anal. calcd. for $C_{22}H_{25}NO_4$: C 71.91, H 6.86, N 3.81. Found: C 71.79, H 6.98, N 3.93.

3-[2-(2-Propionyl-4,5-dimethoxyphenyl)ethylamino]-1-phenyl-but-2-en-1-one (3d). Yield 77%, mp 65-68°C, ^{1}H-NMR: 1.19(t, 3H, J=7), 1.85(s, 3H), 2.93(q, 2H, J=7), 3.07(t, 2H, J=6.4), 3.67(q, 2H, J=6.4), 3.86(s, 3H), 3.90(s, 3H), 5.57(s, 1H), 6.78(s, 1H), 7.24(s, 1H), 7.36-7.83(m, 5H), 11.35(s, 1H,NH); ^{13}C-NMR: 202.5 (Ar-*C*=O), 187.2 (N-C=C-*C*=O), 165.4 (NH-*C*=C), 151.3, 146.9, 140.4, 133.4, 130.3, 129.1, 128.1, 126.8, 115.3, 112.3, 91.8 (NH-C=*C*), 55.8, 55.7, 44.7, 35.7, 33.9, 19.2, 8.5. MS m/z: 381 (M+); Anal. calcd. for $C_{23}H_{27}NO_4$: C 72.42, H 7.13, N 3.67. Found: C 72.55, H 7.25, N 3.79.

3-[2-(2-Acetyl-4,5-dimethoxyphenyl)ethylamino]-cyclohex-2-enone (5a). Yield 70%, mp 149-152°C, ^{1}H-NMR: 1.88-1.96(m, 2H), 2.28(t, 4H, J=3.6), 2.62 (s, 3H), 3.03(t, 2H, J=6.6), 3.34(q, 2H, J=6.6), 3.93(s, 6H), 5.09(s, 1H), 6.39(s, 1H,NH), 6.74(s, 1H), 7.17(s, 1H); ^{13}C-NMR: 201.8 (Ar-*C*=O), 197.0 (N-C=C-*C*=O), 164.7 (NH-*C*=C), 152.2, 146.9, 133.8, 130.2, 113.7, 112.4, 96.1 (NH-C=*C*), 56.1, 56.0, 45.0, 36.4, 31.5, 29.5, 29.4, 21.9. MS m/z: 317 (M+); Anal. calcd. for $C_{18}H_{23}NO_4$: C 68.12, H 7.30, N 4.41. Found: C 68.23, H 7.43, N 4.53.

3-[2-(2-Benzoyl-4,5-dimethoxyphenyl)ethylamino]-cyclohex-2-enone (5b). Yield 71%, mp 54-58°C, ^{1}H-NMR: 1.92(m, 2H), 2.26(t, 2H, J=6.5), 2.36(t, 2H, J=6.4), 2.92(t, 2H, J=5.7), 3.35(m, 2H), 3.77(s, 3H), 3.96(s, 3H), 5.10(s, 1H), 6.78(s, 1H,NH), 6.81(s, 1H), 6.86(s, 1H), 7.49-7.84(m, 5H); ^{13}C-NMR: 198.3 (Ar-*C*=O), 197.2 (N-C=C-*C*=O), 165.1 (NH-*C*=C), 151.6, 146.5, 137.7, 133.6, 133.2, 130.7, 130.2, 128.5, 112.9, 112.8, 96.1 (NH-C=*C*), 56.1, 56.0, 44.9, 36.5, 31.5, 29.5, 22.0, 14.2. MS m/z: 379 (M+); Anal. calcd. for $C_{23}H_{25}NO_4$: C 72.80, H 6.64, N 3.69. Found: C 72.93, H 6.76, N 3.81.

3-[2-(2-Acetyl-4,5-dimethoxyphenyl)ethylamino]-5,5-dimethyl-cyclohex-2-enone (5c). Yield 70%, mp 71-75°C, ^{1}H-NMR: 1.01(s, 6H), 2.11(s, 2H), 2.16(s, 3H), 2.61(s, 2H), 3.02(t, 2H, J=5.3), 3.34(q, 2H, J=5), 3.91(s, 3H), 3.93(s, 3H), 5.06(s, 1H), 6.37(s, 1H,NH), 6.74(s, 1H), 7.16(s, 1H); ^{13}C-NMR: 201.9 (Ar-*C*=O), 196.6 (N-C=C-*C*=O), 163.2 (NH-*C*=C), 152.2, 147.0, 133.9, 130.3, 113.8, 112.5, 94.8 (NH-C=*C*), 56.2, 56.1, 50.3, 45.2, 43.3, 32.7, 31.7, 29.5, 28.3. MS m/z: 345 (M+); Anal. calcd. for $C_{20}H_{27}NO_4$: C 69.54, H 7.88, N 4.05. Found: C 69.68, H 7.99, N 4.18.

3-[2-(2-Propionyl-4,5-dimethoxyphenyl)ethylamino]-5,5-dimethyl-cyclohex-2-enone (5d). Yield 65%, mp 115-118°C, ^{1}H-NMR: 1.02(s, 6H), 1.22(t, 3H, J=7), 2.13(s, 4H), 2.95(q, 4H, J=7), 3.32-3.39(m, 2H), 3.92(s, 3H), 3.93(s, 3H), 5.07(s, 1H), 6.36(s, 1H,NH), 6.75(s, 1H), 7.14(s, 1H); ^{13}C-NMR: 205.2 (Ar-*C*=O), 196.6 (N-C=C-*C*=O), 163.1 (NH-*C*=C), 152.0, 147.2, 133.2, 130.6, 113.7, 111.7, 94.9 (NH-C=*C*), 56.2, 56.1, 50.4, 45.1, 43.3, 34.6, 32.7, 31.6, 28.3, 8.6. MS m/z: 359 (M+); Anal. calcd. for $C_{21}H_{29}NO_4$: C 70.17, H 8.13, N 3.90. Found: C 70.29, H 8.25, N 4.12.

3-[2-(2-Benzoyl-4,5-dimethoxyphenyl)ethylamino]-5,5-dimethyl-cyclohex-2-enone (5e). Yield 68%, mp 50-55°C, ^{1}H-NMR: 0.99(s, 3H), 1.00(s, 3H), 2.16(s, 2H), 2.20(s, 2H), 2.93(t, 2H, J=5.7), 3.38 (q, 2H, J=6.7), 3.78(s, 3H), 3.97(s, 3H), 5.08(s, 1H), 6.62(s, 1H,NH), 6.82(s, 1H), 6.87(s, 1H), 7.50-7.83(m, 5H); ^{13}C-NMR: 198.3 (Ar-*C*=O), 196.6 (N-C=C-*C*=O), 163.3 (NH-*C*=C), 151.6, 146.5, 137.8, 133.6, 133.2, 130.7, 130.3, 128.5, 113.0, 112.9, 94.9 (NH-C=*C*), 56.1, 50.4, 45.0, 43.2, 32.7, 31.1, 28.3. MS m/z: 407 (M+); Anal. calcd. for $C_{25}H_{29}NO_4$: C 73.69, H 7.17, N 3.44. Found: C 73.82, H 7.29, N 3.56.

2-Acetyl-3-[2-(2-acetyl-4,5-dimethoxyphenyl)ethylamino]-cyclohex-2-enone (6a). Yield 10%, mp 160-163°C, ^{1}H-NMR: 1.78(q, 2H, J=6), 2.30(t, 2H, J=6.9), 2.47(t, 2H, J=6), 2.48(s, 3H), 2.57(s, 3H), 3.12(t, 2H, J=6.6), 3.65(q, 2H, J=6), 3.90(s, 3H), 3.92(s, 3H), 6.74(s, 1H), 7.26(s, 1H), 12.64(s, 1H,NH); ^{13}C-NMR: 200.9 (Ar-*C*=O), 199.3 (N-C=C-*C*O-C=O), 194.9 (N-C=C-*C*=O), 173.0 (NH-*C*=C), 151.9, 147.0, 133.2, 128.7, 115.1, 113.7, 108.7 (NH-C=*C*), 56.1, 44.8, 38.3, 35.1, 32.7, 29.1, 26.6, 19.7. MS m/z: 359 (M+); Anal. calcd. for $C_{20}H_{25}NO_5$: C 66.84, H 7.01, N 3.90. Found: C 66.96, H 7.12, N 4.13.

2-Acetyl-3-[2-(2-acetyl-4,5-dimethoxyphenyl)ethylamino]-5,5-dimethyl-cyclohex-2-enone (6b). Yield 10%, mp 150-151°C, ^{1}H-NMR: 0.94(s, 6H), 2.18(s, 2H), 2.31(s, 2H), 2.49(s, 3H), 2.57(s, 3H), 3.12(t, 2H, J=6.6), 3.65(q, 2H, J=6), 3.90(s, 3H), 3.92(s, 3H), 6.74(s, 1H), 7.26(s, 1H), 12.74(s, 1H,NH); ^{13}C-NMR: 200.5 (Ar-*C*=O), 199.3 (N-C=C-*C*O-C=O), 194.5 (N-C=C-*C*=O), 171.9 (NH-*C*=C), 151.9, 147.1, 133.2, 128.7, 115.2, 113.8, 107.7 (NH-C=*C*), 56.1, 56.0, 51.9, 44.8, 39.9, 35.1, 32.7, 30.3, 29.1, 28.2. MS m/z: 387 (M+); Anal. calcd. for $C_{22}H_{29}NO_5$: C 68.20, H 7.54, N 3.61. Found: C 68.32, H 7.66, N 3.73.

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