Tetrahedron 69 (2013) 4586–4590

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A study on the regioselectivity in N,C-acylation of β-enamino-esters

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ARTICLE INFO

Article history:
Received 21 January 2013
Received in revised form 19 March 2013
Accepted 4 April 2013
Available online 10 April 2013

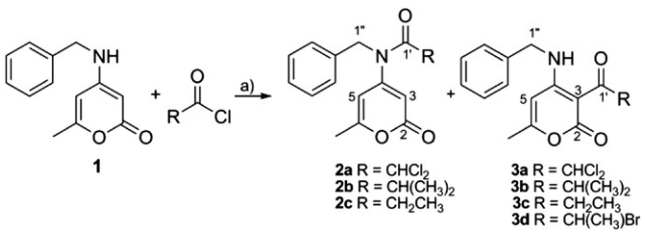
Keywords:
Regioselectivity
N,C-Acylation
β-Enamino-ester
Amino pyrone

ABSTRACT

With the aim to produce the new corresponding amide, amino pyrone **1** [=4-(benzylamino)-6-methyl-2*H*-pyran-2-one] was acylated in dichloromethane in the presence of triethylamine, obtaining an unexpected mixture of *N*- and *C*-acyl products in a 60:40 ratio, respectively. The regioselective investigation was enlarged by using a series of organic bases and taking into account both solvent effects and acyl halide structure. Conditions able to give pure amides or pure *C*-acyl products were established. The study also includes the reactivity of a β-enamino-ester with NH group involved in an intramolecular hydrogen bond, where pure *C*-acyl products were obtained.

1. Introduction

In our recent synthesis of potential antiviral agents, we became interested in producing new amides by acylation of 4-(benzylamino)-6-methyl-2*H*-pyran-2-one (**1**, Scheme 1). Attempts to obtain suitable amides by using an acyl chloride in the presence of triethylamine, resulted in the expected products by N-acylation, but in a mixture with *C*-acyl compounds. These results suggested that we look further into the N,C-acylation selectivity for the ambidentate amino pyrone, whose reactivity is poorly known. In fact, despite recent interest in amino-pyrone chemistry as precursors in the synthesis of natural products,[1–4] only an old theoretical study on their N-basicity was reported.[5] By a general point of view, 4-amino pyrones can be regarded cyclic conjugated β-enamino esters that can act as 1,3-dielectrophiles or as nucleophilic reagents.[6]



Scheme 1. N,C-acylation of amino pyrone **1**. Reagents and conditions: a) suitable base (2.5 equiv) acyl chloride (2.0 equiv), suitable solvent, 0 °C → rt, 18 h, 75–90% yield. Arbitrary numbering is for convenience.

We report here an investigation of the regioselectivity by changing the organic base, the solvent polarity, and acyl agent structure, establishing the best conditions to drive the production of pure regioisomeric products.[7]

2. Results and discussion

By following the general procedure for producing amides by the reaction of an amine with acyl chloride in the presence of an organic base (to trap the formed HCl),[8] amino pyrone **1** was treated with dichloroacetyl chloride. Unexpectedly, a mixture of products containing the desired amide **2a** and **3a** in a 60:40 ratio was obtained, products deriving from N- and C-acylation, respectively (Scheme 1). The structural assignment of the two regioisomers was based on extensive NMR analysis (Experimental) and by comparison of values for C=O stretching deduced by experimental and DFT calculated IR spectra (Table 1).

It was reported that the reaction of primary or secondary amines with dichloroacetyl chloride in the presence of triethylamine gave N-acylation, producing dichloroacetamido derivatives in high yields supposedly via dichloroketene $Cl_2C{=}C{=}O$, which reacted

Table 1
Experimental and DFT calculated values for C=O stretching in regioisomers **2a** and **3a**

Compound	C(2)=O		C(1′)=O	
	Exper. (cm^{-1})	Calcd (cm^{-1})	Exper. (cm^{-1})	Calcd (cm^{-1})
2a	1737	1759	1693	1694
3a	1704	1712	1616	1622

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http://dx.doi.org/10.1016/j.tet.2013.04.012

with the more nucleophilic nitrogen centre.[9] C-Acylation is also possible by the involvement of a zwitterionic resonance form, where the charged *C*-nucleophile can react with acyl chloride (Fig. 1). This is in line with the Klopman–Salem concept that hard–hard interactions are charge controlled (and soft–soft interactions are orbital controlled).[10]

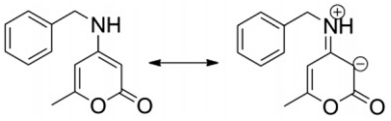


Fig. 1. Two resonance forms of amino pyrone **1**.

A further investigation took into account a series of organic bases, chosen in order to cover a range of different basicity, as reported in Table 2.

Table 2
Selectivity in N,C-dichloroacetylation of amino pyrone **1** by changing the base (in CH_2Cl_2 at 0 °C for 18 h, yield 89%) to give *N*-acyl **2a** and *C*-acyl **3a** products

Base[a]	% **2a**[b]	% **3a**[b]
Pyridine	0	100
4-Methyl-pyridine	0	100
1-Methyl-imidazole	0	100
2,4,6-Trimethyl-pyridine	48	52
1,2-Dimethyl-imidazole	0	100
TMDM	[c]	[c]
Triethanolamine	[c]	[c]
Tributylphosphine	0	100
DABCO	100	0
TMED	66	34
DMAP	0	100
Triethylamine	60	40
DIPEA	90	10
DBU	100	0
No base	0	100

[a] TMDM=*N*,*N*,*N*′,*N*′-tetramethyldiaminomethane, DABCO=1,4-diazabicyclo[2.2.2]octane, TMED=*N*,*N*,*N*′,*N*′-tetramethyl-ethylenediamine, DMAP=4-(dimethylamino)pyridine, DIPEA=*N*-ethyldiisopropylamine, DBU=1,8-diazabicyclo[5.4.0]undec-7-ene.
[b] The *N*- and C-acylation ratio was evaluated in the crude reaction mixture by the relative signal integrals in ^{1}H NMR spectrum recorded in $CDCl_3$, at δ=4.55 ppm (d, $PhCH_2$) in **3a** and δ=4.90 ppm (s, $PhCH_2$) in **2a**.
[c] No products were obtained; starting amino pyrone **1** was practically recovered in quantitative amount.

By replacing triethylamine with DBU, DABCO, and diisopropylethylamine (DIPEA), the expected amide **2a** were obtained in pure form, in agreement with the probable involvement of the soft dichloroketene electrophile, produced by dehydrochlorination of dichloroacetyl chloride induced by hindered and non-nucleophile bases.

An interesting completely reversed selectivity was given by using pyridine, 4-methylpyridine, 4-dimethylaminopyridine (DMAP), 1-methylimidazole, and 1,2-dimethylimidazole) and tributylphosphine, to produce pure *C*-acyl product **3a**. It can be explained by the hard–hard interaction between the pyrone substrate in its zwitterionic form and a probable *N*-dichloroacetyl pyridinium species acting as electrophile. It is in line with the report of acylammonium salts isolated from the reaction of acyl chlorides and amines including pyridine, DMAP, picoline, and triethylamine.[11] The low selectivity observed by using triethylamine, TMED, and 2,4,6-trimethylpyridine is attributable to the involvement of both mechanisms.[8] In order to rationalize the effect of base structure, their proton affinity, defined as the tendency of a base to accept a proton in gas phase and reported as the difference between the energy values for protonated (BH^+) form and free base (B),[12] has been evaluated by density functional theory (DFT) calculations, but no correlation was found. It is noteworthy that carrying out the reaction without triethylamine and any other bases, pure *C*-acyl compound **3a** was produced. This evidence is in agreement with the nucleophile attack of the zwitterionic pyrone with the electrophile carbonyl group present both in dichloroacetyl chloride and dichloroacetyl pyridinium species, as well as with the absence of the dichloroketene, whose formation requires the base.

The evaluation of solvent effect was also investigated in two cases of highly selective acylation: by employing pyridine, to give pure *C*-acyl product **3a** and by using DBU producing the *N*-acyl compound **2a**. The replacement of dichloromethane with solvents having different polarity did not affect the selectivity in the presence of pyridine. On the contrary, with DBU the selectivity in N,C-acylation was lost in toluene or acetonitrile, whereas it was fully reversed in acetone (Table 3).

Table 3
Selectivity in N,C-dichloroacetylation of amino pyrone **1** using pyridine or DBU by changing the solvent (at 0 °C for 18 h, yield 89%) to give *N*-acyl **2a** and *C*-acyl **3a** products

Solvent	Pyridine		DBU	
	% **2a**[a]	% **3a**[a]	% **2a**[a]	% **3a**[a]
Dichloromethane	0	100	100	0
Toluene	0	100	60	40
Acetonitrile	0	100	64	36
Acetone	0	100	0	100

[a] The *N*- and C-acylation ratio was evaluated in the crude reaction mixture by the signal integrals in ^{1}H NMR spectrum recorded in $CDCl_3$, at δ=4.55 ppm (d, $PhCH_2$) in **3a** and δ=4.90 ppm (s, $PhCH_2$) in **2a**.

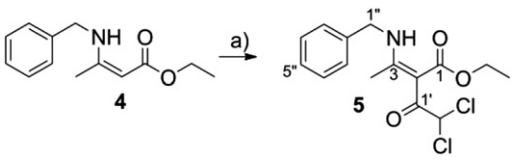
It is evident that the presence of two electronegative atoms in dichloroacetyl chloride is able to increase the positive charge on the C=O group, so that to increase its electrophilicity. In order to expand the investigation, other acyl halides were studied in the reactions carried out in dichloromethane with pyridine or DBU. The results reported in Table 4 indicate that selectivity is not affected by the acyl structure.

Table 4
Selectivity in N,C-acylation of amino pyrone **1** using pyridine or DBU by changing the acyl halide (in CH_2Cl_2 at 0 °C for 18 h, yields 78–90%)

Acyl halide	Pyridine		DBU	
	% *C*-Acyl product[a]	% *N*-Acyl product[a]	% *C*-Acyl product[a]	% *N*-Acyl product[a]
Dichloroacetyl chloride	100	0	0	100
Propionyl chloride	93	7	12	88
Isobutyryl chloride	100	0	0	100
2-Bromo-propionyl bromide	100	0	[b]	[b]

[a] The ratio of N- and C-acylation was evaluated in the crude reaction mixture by the signal integrals of benzylic protons in ketones and amides in ^{1}H NMR spectrum recorded in $CDCl_3$.
[b] No products were obtained and tars were recovered.

The regioselectivity was further evaluated on (*Z*)-ethyl 3-(benzylamino)but-2-enoate (**4**). It was treated in dichloromethane with dichloroacetyl chloride in the presence of different bases (Scheme 2). Each reaction, carried out with triethylamine, pyridine, DBU or without any base, always gave a complete regioselectivity in favor of the *C*-acyl product **5**. The (*Z*)-configuration of β-enamino ester **4** was secured by an intramolecular hydrogen bond between NH and C=O groups and forming a stable six membered ring, as established by the presence of a broad singlet at 8.94 ppm in ^{1}H NMR spectrum of **4** recorded in $CDCl_3$. Otherwise the enamino-like double bond present in the structure of amino pyrone **1** has an (*E*)-configuration avoiding any similar reactivity. In addition, the presence of the benzyl moiety may have inhibited N-acylation as a result of steric hindrance.[13]



Scheme 2. Acylation of β-enamino ester 4 by using different bases. Reagents and conditions: a) triethylamine, or pyridine, or DBU, or no base, dichloroacetyl chloride, CH_2Cl_2, 0 °C → rt, 18 h, 78–90% yield.

3. Conclusions

The acylation of 4-(benzylamino)-6-methyl-2*H*-pyran-2-one with dichloroacetyl chloride in dichloromethane was investigated by using different organic bases. It produced the regioisomers by N- and C-attack, with a high selectivity in favor of the expected amide by using DABCO, DBU, and DIPEA, and fully reversed reactivity giving *C*-acyl product in the presence of pyridine, 4-methylpyridine, DMAP, 1-methylimidazole, 1,2-dimethylimidazole, and tributylphosphine, or in absence of any bases. Both the solvent polarity and the acyl halide structure did not effectively affect the selectivity. The study on an (*Z*)-acyclic β-enamino ester taken as a model compound, gave only the corresponding *C*-acyl product, probably due to the involvement of a stable intramolecular hydrogen bond, as established by NMR analysis. The reactivity here investigated represents an effective and versatile access to practically pure regioisomers, otherwise difficult to be produced.

4. Experimental section

4.1. General

All evaporations were carried out at reduced pressure at room temperature. Yields are given on the reacted compounds. Solvents and reagents were purchased from Sigma–Aldrich Europe and from Alfa Aesar and were used without purification. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF254 and flash chromatography (FC) was carried on Merck silica gel (Si-60, 15±25 μm). Preparative TLC was realized on 20×20 cm Merck Kieselgel 60 F254 0.5 mm plates. Ultrasound bath Badelin Sonorex RK510, 35 KHz, 160 W was used for the synthesis of compound **4**. IR spectra were acquired by FT-IR Equinox 55 Bruker, equipped with ATR device in zinc selenide. NMR spectra were recorded by an Avance 400Bruker spectrometer: ^{1}H at 400 MHz and ^{13}C at 100 MHz in $CDCl_3$. δ values are reported in parts per million relative to the solvent residual signals δ_H=7.25 and δ_C=77.00 ppm for $CDCl_3$, relative to $SiMe_4$ (=0 ppm); *J* values in Hertz. ^{13}C NMR assignments come from heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments. For NMR assignments a numbering for convenience was adopted. Electron impact (EI) mass spectra (*m*/*z*; rel%) and high-resolution EI data (±0.003) were taken with a Kratos-MS80 mass spectrometer with a home-built computerized acquisition software. Electrospray ionization (ESI)-MS mass spectra and tandem fragmentation spectra (MS/MS) were taken with a Bruker Esquire-LC spectrometer equipped with an electrospray ion source used in positive or negative ion mode by direct infusion of a methanolic solution of the sample, under the following conditions: source temperature 300 °C, drying gas N_2, 4 L/min, positive ion mode, ISV 4 kV, OV 38.3 V, scan range *m*/*z* 100–1000. Quantum chemical calculations were performed using the Gaussian 03W revision E.01 package program set.[14] The basis set of choice was 6–31 G(d) for geometry optimization and the optimized structural parameters were employed in the vibrational energy calculations at the DFT levels to characterize all stationary points as minima. Then, vibrational averaged nuclear positions were adopted for harmonic vibrational energy calculations, resulting in IR wavenumbers together with intensities and force constants. For each optimized structure, no imaginary wavenumber modes were obtained, proving that a local minimum on the potential energy surface was actually found. The computed wavenumbers were scaled by factor 0.9613, suggested for B3LYP/6–31G(d) calculations.[15] Similarly, proton affinity of the organic bases was calculated at DFT B3LYP/aug-ccpVDZ level of theory.

*4.1.1. 4-(Benzylamino)-6-methyl-2H-pyran-2-one (**1**).* A mixture containing 6-methyl-2-oxo-2*H*-pyran-4-yl 4-tosylate (280.3 mg, 1 mmol), benzylamine (120 μL, 1.1 mmol), and Et_3N (210 μL, 1.5 mmol) in absolute ethanol (60 mL) was stirred at room temperature for 60 h monitoring by TLC (hexane/ethyl acetate/Et_3N=20:79:1). After concentration in vacuo, purification by flash chromatography using hexane/ethyl acetate by gradient, gave the title compound **1** (118 mg, 55%) as viscous transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47–7.14 (5H, m, C_6H_5–), 5.57 (1H, s, H-3), 5.16 (1H, br s, NH), 4.99 (1H, s, H-5), 4.27 (2H, d, *J* 5.2 Hz, H-1′), 2.12 (3H, s, Me–C(6)). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.5 (C-4), 161.3 (C-2 and C-6), 136.7 (C-2′), 129.0 (C-4′ and C-6′), 127.9 (C-3′ and C-7′), 127.5 (C-5′), 99.2 (C-5), 81.11 (C-3), 46.8 (C-1′), 19.9 (Me–C(6)). EI-MS *m*/*z* (%): 215 ([M$^+$•], 40), 187 (30), 106 (22); HR(EI) MS: 215.09448 ($C_{13}H_{13}NO_2$, calcd 215.09463). The data are consistent with the ones reported by McLaughlin et al.[3]

*4.1.2. (Z)-Ethyl 3-(benzylamino)but-2-enoate (**4**).* A mixture of ethyl acetoacetate (0.5 mL, 3.9 mmol), benzylamine (0.43 mL, 3.9 mmol), and acetic acid (25 μL, 0.44 mmol) was placed in an ultrasound bath at a temperature never exceeding 30 °C, for 1 h. Later ethanol (10 mL) was added, the resulting solution was dried on anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give pure product (850 mg, quantitative yield). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.94 (1H, br s), 7.31–7.20 (5H, m), 4.52 (1H, s), 4.42 (2H, d, *J* 6.4 Hz), 4.09 (2H, q, *J* 7.0 Hz), 1.9 (3H, s), 1.25 (3H, t, *J* 7.0 Hz). The data are consistent with the ones reported by Brandt et al.[16]

4.2. General procedure for the synthesis of compounds 2a–c, 3a–d and 5

To a solution of compound **1** (5 mg, 0.02 mmol) or **4** (5 mg, 0.02 mmol) dissolved in anhydrous CH_2Cl_2 (0.5 mL), the suitable amine (0.05 mmol) was added and the solution cooled at 0 °C for 30 min. The proper acyl chloride (0.04 mmol) was slowly added at this temperature. The mixture was stirred at room temperature for 18 h monitoring by TLC (hexane/ethyl acetate=6:4). After concentration in vacuo, the crude products were analyzed by ^{1}H NMR analysis.

*4.2.1. N-Benzyl-2,2-dichloro-N-(6-methyl-2-oxo-2H-pyran-4-yl) acetamide (**2a**).* Yield 82%. Oil, R_f (40% EtOAc/hexane) 0.31. ν_{max} (neat) 3070–2850 (br), 1737, 1693, 1641, 1562, 1215, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38–7.30 (3H, m, H-4″, H-5″, and H-6″), 7.23–7.17 (2H, m, H-3″ and H-7″), 6.19 (1H, s, H-2′), 5.93 (1H, s, H-3), 5.88 (1H, s, H-5), 4.90 (2H, s, H-1″), 2.26 (3H, s, Me–C(6)). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5 (C-1′), 164.9 and 164.8 (C-2 and C-6), 154.7 (C-4), 134.6 (C-2″), 128.7 (C-4″ and C-6″), 127.6 (C-3″ and C-7″), 126.6 (C-5″), 108.6 (C-5), 103.1 (C-3), 63.3 (C-2′), 51.5 (C-1″), 20.6 (Me–C(6)). ESI-MS (positive mode): 348 ([M+Na]$^+$). EI-MS *m*/*z* (%): 325 ([M$^+$•], 4), 214 (10), 91 (100); HR(EI) MS: 325.0267 ($C_{15}H_{13}^{35}Cl_2NO_3$, calcd 325.02725).

*4.2.2. 4-(Benzylamino)-3-(2,2-dichloroacetyl)-6-methyl-2H-pyran-2-one (**3a**).* Yield 89%. White solid (from hexane/ethyl acetate), mp 94–95 °C, R_f (40% EtOAc/hexane) 0.44. ν_{max} (neat) 3232–2930 (br), 1704, 1659, 1616, 1568, 1498, 1456, 1363, 1338, 1296, 1230,

700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.43 (1H, br s, NH), 7.67 (1H s, H-2′), 7.46–7.32 (3H, m, H-4″, H-5″, and H-6″), 7.32–7.26 (2H, m, H-3″ and H-7″), 5.93 (1H, s, H-5), 4.57 (2H, d, *J* 5.6 Hz, H-1″), 2.21 (3H, s, Me–C(6)). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 188.4 (C-1′), 166.9 and 166.8 (C-2 and C-6), 163.2 (C-4), 135.2 (C-2″), 129.1 (C-4″ and C-6″), 127.0 (C-5″), 126.9 (C-3″ and C-7″), 95.3 (C-5), 90.4 (C-3), 69.8 (C-2′), 47.0 (C-1″), 20.6 (Me–C(6)). EI-MS *m*/*z* (%): 325 ([$M^{+\bullet}$], 4), 290 (16), 254 (23), 242 (86); HR(EI)MS: 325.02575 ($C_{15}H_{13}Cl_2NO_3$, calcd 325.02725).

*4.2.3. N-Benzyl-N-(6-methyl-2-oxo-2H-pyran-4-yl)isobutyramide (**2b**).* Yield 78%. Oil, R_f (40% EtOAc/hexane) 0.29. ν_{max} (neat) 2957, 2854, 1720, 1676, 1639, 1556, 1452, 1414, 1379, 1319, 1198, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41–7.26 (3H, m, H-4″, H-5″, and H-6″), 7.20–7.13 (2H, m, H-3″ and H-7″), 5.99 (1H, s, H-3), 5.77 (1H, s, H-5), 4.85 (2H, s, H-1″), 2.83 (1H, septet, *J* 6.6 Hz, H-2′), 2.23 (3H, s, Me–C(6)), 1.15 (6H, d, *J* 6.6 Hz, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177. 8 (C-1′), 162.7 (C-2 and C-6), 157.2 (C-4), 136.4 (C-2″), 128.5 (C-4″ and C-6″), 127.1 (C-5″), 127.0 (C-3″ and C-7″), 105.5 (C-5), 103.3 (C-3), 51.4 (C-1″), 32.0 (C-2′), 20.6 (Me–C(6)), 19.0 (two C-3′). ESI-MS (positive mode): *m*/*z* 286 ([M+H]$^+$), 308 ([M+Na]$^+$), 593 ([2M+Na]$^+$); MS/MS (286): *m*/*z* 216 ([M+H−C_4H_6O]$^+$). EI-MS *m*/*z* (%): 285 ([$M^{+\bullet}$], 17), 214 (47), 91 (75), 43 (100); HR(EI)MS: 285.13607 ($C_{17}H_{19}NO_3$, calcd 285.13649).

*4.2.4. 4-(Benzylamino)-3-isobutyryl-6-methyl-2H-pyran-2-one (**3b**).* Yield 79%. Oil, R_f (40% EtOAc/hexane) 0.40. ν_{max} (neat) 2970, 2933, 2873, 1707, 1658, 1603, 1560, 1495, 1454, 1379, 1342, 1232, 1157, 1011, 918, 866, 806, 750, 737, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.03 (1H, br s, NH), 7.42–7.31 (3H, m, H-4″, H-5″, and H-6″), 7.30–7.24 (2H, m, H-3″ and H-7″), 5.81 (1H, s, H-5), 4.50 (2H, d, *J* 5.6 Hz, H-1″), 2.16 (3H, s, Me–C(6)), 1.11 (6H, d, *J* 6.7 Hz, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 208. 8 (C-1′), 165.5 and 165.1 (C-2 and C-6), 162.7 (C-4), 136.0 (C-2″), 128.5 (C-4″ and C-6″), 127.4 (C-3″ and C-7″), 127.3 (C-5″), 94.5 (C-5), 93.2 (C-3), 46.7 (C-1″), 37.7 (C-2′), 20.6 (Me–C(6)), 18.5 (two C-3′). ESI-MS (positive mode): *m*/*z* 286 ([M+H]$^+$), 308 ([M+Na]$^+$); MS/MS (286): *m*/*z* 268 ([M+H−H_2O]$^+$), 216 ([M+H−C_4H_6O]$^+$). EI-MS *m*/*z* (%): 285 ([$M^{+\bullet}$], 9), 242 (63), 194 (42), 91 (100); HR(EI)MS: 285.13652 ($C_{17}H_{19}NO_3$, calcd 285.13649).

*4.2.5. N-Benzyl-N-(6-methyl-2-oxo-2H-pyran-4-yl)propionamide (**2c**).* Yield 73%. Colorless oil, R_f (40% EtOAc/hexane) 0.27. ν_{max} (neat) 2952, 2854, 1720, 1676, 1639, 1556, 1452, 1414, 1379, 1319, 1198, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37–7.27 (3H, m, H-4″, H-5″, and H-6″), 7.20–7.13 (2H, m, H-3″ and H-7″), 6.13 (1H, s, H-3), 5.77 (1H, s, H-5), 4.88 (2H, s, H-1″), 2.43 (2H, q, *J* 7.4 Hz, H-2′), 2.23 (3H, s, Me–C(6)), 1.16 (3H, t, *J* 7.4 Hz, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.1 (C-1′), 162.4 and 164.3 (C-2 and C-6), 157.2 (C-4), 136.1 (C-2″), 127.9 (C-4″ and C-6″), 127.1 (C-5″), 126.8 (C-3″ and C-7″), 103.2 (C-5), 51.5 (C-1″), 28.5 (C-2′), 20.6 (Me–C(6)), 18.1 (C-3′). ESI-MS (positive mode): *m*/*z* 272 ([M+H]$^+$), 294 ([M+Na]$^+$); MS/MS (272): *m*/*z* 216 ([M+H−C_3H_4O]$^+$). EI-MS *m*/*z* (%): 271 ([M^+], 33), 242 (66), 180 (20), 91 (100); HR(EI)MS: 271.12064 ($C_{16}H_{17}NO_3$, calcd 271.12084).

*4.2.6. 4-(Benzylamino)-6-methyl-3-propionyl-2H-pyran-2-one (**3c**).* Yield 75%. Oil, R_f (40% EtOAc/hexane) 0.41. ν_{max} (neat) 3370–2830 (br), 1703, 1657, 1603, 1560, 1495, 1454, 1360, 1340, 1234, 1176, 1009, 914, 814, 737, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.97 (1H, br s, NH), 7.42–7.30 (3H, m, H-4″, H-5″, and H-6″), 7.28–7.23 (2H, m, H-3″ and H-7″), 5.81 (1H, s, H-5), 4.51 (2H, d, *J* 5.8 Hz, H-1″), 3.07 (2H, q, *J* 7.2 Hz, H-2′), 2.16 (3H, s, CH_3–C(6)), 1.10 (3H, t, *J* 6.7 Hz, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 204.7 (C-1′), 165.6 and 165.5 (C-2 and C-6), 161.5 (C-4), 136.3 (C-2″), 128.5 (C-4″ and C-6″), 127.2 (C-5″), 127.1 (C-3″ and C-7″), 94.7 (C-5), 94.0 (C-3), 45.2 (C-1″), 37.3 (C-2′), 20.7 (Me–C(6)), 10.1 (C-3′). ESI-MS (positive mode): *m*/*z* 272 ([M+H]$^+$), 294 ([M+Na]$^+$). 564 ([2M+Na]$^+$); MS/MS (272): *m*/*z* 216 ([M+H−C_3H_4O]$^+$); MS^3 (216): *m*/*z* 138 ([M+H−C_6H_6]$^+$). EI-MS *m*/*z* (%): 271 ([$M^{+\bullet}$], 33), 242 (71), 180 (21), 91 (100); HR(EI)MS: 271.12072 ($C_{16}H_{17}NO_3$, calcd 271.12084).

*4.2.7. 4-(Benzylamino)-3-(2-bromopropanoyl)-6-methyl-2H-pyran-2-one (**3d**).* Yield 85%. Pale yellow oil, R_f (40% EtOAc/hexane) 0.41. ν_{max} (neat) 3300–2800 (br), 1706, 1657, 1604, 1562, 1495, 1454, 1367, 1338, 1242, 1167, 1012, 920, 806, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.69 (1H, br s, NH), 7.42–7.32 (3H, m, H-4″, H-5″, and H-6″), 7.29–7.26 (2H, m, H-3″ and H-7″), 6.13 (1H, q, *J* 6.7 Hz, H-2′), 5.87 (1H, s, H-5), 4.53 (d, *J* 5.7 Hz, H-1″), 2.19 (3H, s, Me–C(6)), 1.79 (2H, d, *J* 6.7 Hz, 3H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197. 2 (C-1′), 166.2 and 166.1 (C-2 and C-6), 162.9 (C-4), 135.6 (C-2″), 128.7 (C-4″and C-6″), 127.1 (C-5″), 127.0 (C-3″ and C-7″), 94.9 (C-5), 91.8 (C-3), 47.7 (C-2′), 46.9 (C-1″), 20.8 (Me–C(6)), 20.4 (C-3′). ESI-MS (positive mode): *m*/*z* 350/352 ([M+H]$^+$), 372/374 ([M+Na]$^+$), 388/390 ([M+K]$^+$); MS/MS (252): *m*/*z* 270 ([M+H−$H^{81}Br$]$^+$), 180 ([M+H−$H^{81}Br$−C_7H_6]$^+$). EI-MS *m*/*z* (%): 349 ([$M^{+\bullet}$], 1.5), 270 (51), 242 (27), 91 (100); HR(EI)MS: 349.02959 ($C_{16}H_{16}^{79}BrNO_3$, calcd 349.03136).

*4.2.8. (Z)-Ethyl 3-(benzylamino)-2-(2,2-dichloroacetyl)but-2-enoate (**5**).* Yield 82%. Yellow oil, R_f (40% EtOAc/hexane) 0.35. ν_{max} (neat) 3068, 2977, 2935, 1703, 1657, 1603, 1562, 1493, 1454, 1340, 1234, 1176, 1009, 914, 814, 735, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.65 (1H, br s, NH), 7.44–7.36 (3H, m, H-4″, H-5″, and H-6″), 7.32–7.22 (2H, m, H-3″ and H-7″), 6.92 (1H, s, H-2′), 4.57 (2H, d, *J* 5.6 Hz, H-1″), 4.25 (2H, q, *J* 7.1 Hz, −OCH_2−), 2.29 (3H, s, C-4), 1.34 (3H, t, *J* 7.1 Hz, CH_3CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.7 (C-1′), 171.3 (C-3), 168.2 (C-1), 135.3 (C-2″), 128.1 (C-4″, and C-6″), 127.6 (C-3″ and C-7″), 127.3 (C-5″), 98.8 (C-2), 71.7 (C-2′), 60.9 (−OCH_2−), 47.8 (C-1″), 17.9 (Me–(C-3)), 13.89 (CH_3−). ESI-MS (positive mode): *m*/*z* 330 ([M+H]$^+$), 352 ([M+Na]$^+$); MS/MS (330): *m*/*z* 284 ([M+H−C_2H_6O]$^+$). EI-MS *m*/*z* (%): 329 ([$M^{+\bullet}$], 2), 246 (55), 91 (100); HR(EI)MS: 329.05801 ($C_{15}H_{17}^{35}Cl_2NO_3$, calcd 329.05855).

Acknowledgements

We are grateful to Mr. A. Sterni and D. Avi for recording mass and FT-IR spectra, respectively.

Supplementary data

Supplementary data associated with this article, including NMR spectra of **2a**–**c** and **3a**–**d** and IR spectra of **2a** and **3a**, can be found in the online version. Supplementary data related to this article can be found at http://dx.doi:10.1016/j.tet.2013.04.012.

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