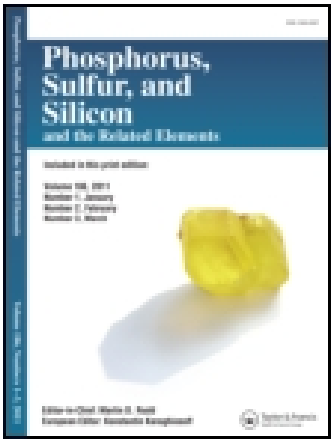

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One-Pot Three-Component Synthesis of β-Acylaminoketones Containing a Thiophene Ring by the Use of Tetrachlorosilane-Zinc Chloride as a Binary Reagent Under Ambient Conditions

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A new route for the synthesis of β-acylaminoketones containing a thiophene ring through multicomponent condensation reaction of different ketones, different aldehydes, and different nitriles with tetrachlorosilane (TCS) and zinc chloride as the binary reagent is described.

Keywords β-Acylaminoketones; binary reagent; tetrachlorosilane; thiophene

INTRODUCTION

β-Acetamidoketones are versatile and potential intermediates and exist in a number of biologically or pharmacologically important derivatives,[1–5] such as nikkomycin or neopolyoxin[3] antibiotics. The best known route for the synthesis of these compounds is the Dakin–West reaction,[6] which includes the condensation of an amino acid with acetic anhydride in the presence of a base via an intermediate azalactone to give the acetamidoketones.[7] According to the previous method, other methods were developed to synthesize β-acetamidoketones through condensation of an aryl aldehyde, acetophenone, and acetyl chloride in acetonitrile in the presence of $CoCl_2$[8a] or morillonite K-10 clay[8b] or SiO_2-H_2SO_4[8c] under thermal conditions, or

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by using $ZrOCl_2.8H_2O$[8d] or $BiCl_3$ generated in situ from BiOCl and acetyl chloride at room temperature.[8e–j] Although these protocols are valuable, they lack the generality to produce arrays of β-amido ketones, and by way of a survey we found only one example of a β-benzamido ketone that had been prepared by this method involving benzonitrile via a long time (36 h).[8d] Concerning the multicomponent reactions methods to produce β-amidoketones, an efficient one is still required.

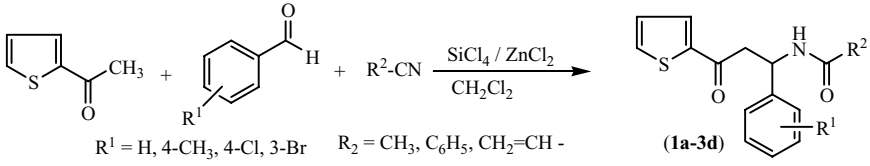
Toward this aim, and in continuation of investigations on the development and applications of new in situ reagents derived from tetrachlorosilane (TCS)[9–11] in organic synthesis, we have developed an efficient, general, and convenient protocol for the one-pot synthesis of β-amidoketones. The reaction proceeds via a three-component reaction of various aldehydes, ketones, and nitriles including alkyl, aryl, and α, β-unsaturated nitriles utilizing the inexpensive and readily available tetrachlorosilane–zinc chloride reagent in dichloromethane at room temperature.

RESULTS AND DISCUSSION

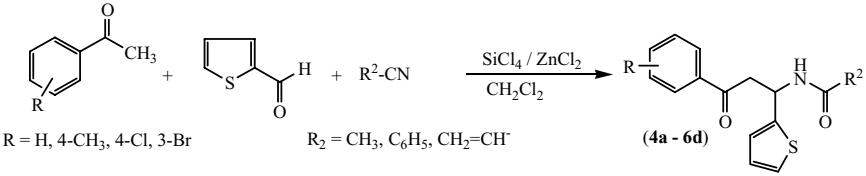
The development of new silane reagents derived from tetrachlorosilane and their use in organic synthesis was applied in the present work. Thus, the scope and limitation of the $SiCl_4$-$ZnCl_2$ combination system with respect to the one-pot three-component reaction of aldehydes, ketones, and nitriles was studied.

The following optimal conditions were found: a mixture of benzaldehyde (10 mmol), 2-acetylthiophene (10 mmol), and acetonitrile (10 mmol) in the presence of $SiCl_4$ (30 mmol) and $ZnCl_2$(30 mmol) in dichloromethane as solvent was stirred at ambient temperature. The reaction mixture proceeded with high selectivity to a single product as detected by thin layer chromatography (TLC), as shown in Scheme 1. The isolated product was identified as *N*-[3-oxo-1-phenyl-3-(thien-2-yl)propyl]acetamide **1a**.

After optimization, a variety of other aromatic aldehydes and aromatic ketones having electron-donating as well as electron-withdrawing substituents were shown to undergo the reaction



SCHEME 1



SCHEME 2

smoothly, giving the desired products in good yields (Schemes 1 and 2). For the one-pot condensation of the aldehyde containing an electron-donating group (CH_3) with 2-acetylthiophene, the reaction time was reduced with increase of the product yield relative to the unsubtituted benzaldehyde; for aldehydes containing electron-withdrawing substituents (Cl, Br), the time of reaction increased and the yield was reduced. In the reaction of thiophene-2-carbaldehyde with acetophenones, it was noticed also that the presence of electron-donating substituents increases the yield with reducing reaction time, but the presence of electron-withdrawing substituents reduces the yield with increasing reaction time (Tables I and II).

The structures of the obtained β-acylaminoketones were elucidated by spectroscopic methods. Thus, their IR spectra showed peaks at $\nu = 3350–3241$, 1685–1655, and 1652–1634 cm^{-1} corresponding to the NH, carbonyl of ($COCH_2$), and amidic carbonyl (CONH) groups, respectively. ^1H NMR spectra of the synthesized products were characterized

TABLE I One-Pot Condensation of Acetylthiophene, Substituted Benzaldehydes, and Different Nitriles Giving the Corresponding β-Acetamidoketones

Entry	R^1	R^2	Product	Time (h)	Yield%
1	H	CH_3	**1a**	10	80
2	4-CH_3	CH_3	**1b**	8	85
3	4-Cl	CH_3	**1c**	11	75
4	3-Br	CH_3	**1d**	12	72
5	H	C_6H_5	**2a**	15	78
6	4-CH_3	C_6H_5	**2b**	12	80
7	4-Cl	C_6H_5	**2c**	16	75
8	3-Br	C_6H_5	**2d**	20	72
9	H	CH_2=CH—	**3a**	16	70
10	4-CH_3	CH_2=CH—	**3b**	15	75
11	4-Cl	CH_2=CH—	**3c**	17	65
12	3-Br	CH_2=CH—	**3d**	18	60

TABLE II One-Pot Condensation of Thiophene-2-carbaldehyde, Substituted Acetophenones, and Different Nitriles Giving the Corresponding β-Acetamidoketones

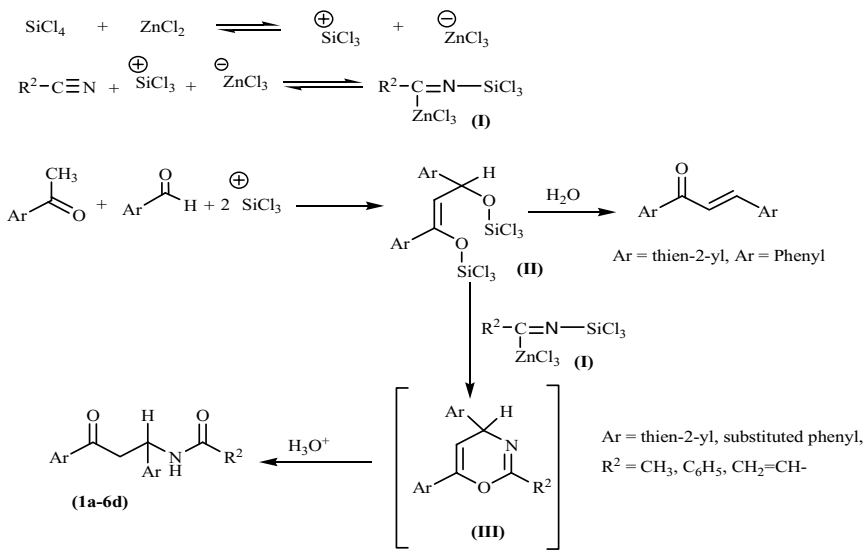
Entry	R	R^2	Product	Time (h)	Yield%
1	H	CH_3	**4a**	8	90
2	4-CH_3	CH_3	**4b**	6	92
3	4-Cl	CH_3	**4c**	10	85
4	4-Br	CH_3	**4d**	12	80
5	H	C_6H_5	**5a**	12	85
6	4-CH_3	C_6H_5	**5b**	10	88
7	4-Cl	C_6H_5	**5c**	14	77
8	4-Br	C_6H_5	**5d**	16	75
9	H	CH_2=CH—	**6a**	14	72
10	4-CH_3	CH_2=CH—	**6b**	12	75
11	4-Cl	CH_2=CH—	**6c**	13	70
12	4-Br	CH_2=CH—	**6d**	15	65

by the presence of two doublet signals at $\delta = 4.00$–3.65 and 3.79–3.34 ppm ($J = 5.60$, 16.20 Hz) for ($COCH_2$) and quartet signals at $\delta = 5.88$–5.26 ppm for CH-protons. The ^{13}C NMR spectrum of compound **1b** showed the characteristic two signals at $\delta = 192.00$ for ketonic (C=O) and at 170.32 for the amidic (CONH) carbonyl groups, at 145.50–127.55 for the $C_{ar}H$, at 47.81 for CHNH, at 45.43 for CH_2CO, and at 26.1 and 21.9 for the two CH_3 groups. Representative results are summarized in Table I.

Following these good results that were obtained, we explored the reaction of thiophene-2-carbaldehyde with different ketones and nitriles. The reaction proceeded with high selectivity, affording β-acylaminoketone derivatives **(4a–6d)** with good yields, as shown in Scheme 2. Representative results are summarized in Table II.

Moreover, to optimize the reaction conditions, the reaction was carried out in various solvents. Dichloromethane (CH_2Cl_2) was found to be the most effective solvent,[12] while donor solvents such as diethyl ether completely inhibited the reaction. Stannous chloride ($SnCl_2$) as a Lewis acid was examined and similar results were obtained, but it was found to be less effective than zinc chloride. It was noticed that no reaction took place in the absence of either $SiCl_4$or $ZnCl_2$ under the same reaction conditions.

The mechanism of the reformation of the Cl_4Si-$ZnCl_2$ system could be explained as follows. The Zn^{2+}-ion atom can accept a halide anion to form a Cl_3Si^+-$ZnCl_3^-$ species[15,9b]. In the presence of this ion-pair, the three-component reaction involving ketone, aldehyde, and nitrile



SCHEME 3

occurs. The cyano group of the nitrile is effectively activated[16] by reacting with Cl_3Si^+-$ZnCl_3^-$ under formation of the intermediate **I**. All of these reactions proceed through the common aldol silyl enolether **II**[13–14] as intermediate, since the Cl_3Si^+-cation attacks the oxygen atom of the aldol to activate the carbonyl group by way of forming Cl_3Si-O-CR_2^+. Support for the formation of the intermediate **II** came from the reaction of 2-acetylthiophene with benzaldehyde in the presence of Cl_3Si^+-$ZnCl_3^-$ but in the absence of any nitrile, which resulted in the formation of 3-phenyl-1-(thien-2-yl)prop-2-en-1-one as the isolated product.[17] Indeed, all intermediates **II** react in essentially identical fashion with the intermediate **I** at room temperature.[18] 4*H*-1,3-Oxazine derivatives **III** are formed, which undergo ring opening during the work-up procedure with aqueous acidic ($p_H = 3$) to give finally the corresponding β-acylaminoketones **(1a-6d)** as shown in Scheme 3.

This approach would eliminate the necessity to prepare the β-chloroketones,[19] which requires the β-acylaminoketone[20] as precursors and also provides an additional diversity. Reasonable results can be obtained for the addition of one position of diversity. Commercial availability of a wide range of nitriles, aldehydes, and methylene ketones makes this a valuable approach for the preparation of highly diversified combinatorial libraries of β-acylaminoketones.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, National Research Center, Cairo, Egypt. Infrared spectra (KBr) were recorded using a Jasco FT/IR-300E spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ using Varian Mercury 300 MHz and Varian Gemini 200 MHz spectrometers with chemical shifts using TMS as standard. Mass spectra were recorded on a GC/MS Finnigan SSQ 7000 spectrophotometer. All reactions were carried out under atmospheric conditions at room temperature. Tetrachlorosilane (TCS) was obtained from commercial sources. Anhydrous zinc chloride was used as obtained from Aldrich. The solvents were distilled and dried before use. Reactions were monitored by TLC on 0.25 mm Merck Silica gel sheets (60 GF 354) (4 × 2 cm), and the spots were detected with UV light.

General Procedure

A mixture of ketone (10 mmol), aldehyde (10 mmol), nitrile (10 mmol), anhydrous $ZnCl_2$ (4.08 g, 30 mmol), and CH_2Cl_2 (20 mL) as solvent was stirred with exclusion of moisture at 25°C for 10 min. Tetrachlorosilane (3.6 mL, 30 mmol) was then added, and the reaction mixture was stirred again for the specified time. The reaction mixture was poured onto ice-cold water (100 mL), neutralized with Na_2CO_3 solution, and extracted with $CHCl_3$ (2 × 50 mL). The extract was dried over anhydrous Na_2SO_4, and the solvent was removed by distillation. Finally the residue was purified by chromatographic methods to obtain the pure products.

N-[3-Oxo-1-phenyl-3-(thien-2-yl)propyl]acetamide (1a)

M.p.: 80–82°C. $R_f = 0.25$ (PE/AcOEt 2:1). IR: $\nu = 3306$ (NH), 3060–3015 (CH, Ar), 2920–2850 (CH_3, CH_2, CH), 1682 (C=O), 1645 (CONH), 1590, 1560, 1515 (C=C, Ar) cm^{-1}. ^{1}H NMR: δ 6.82–7.75 (m, 9H, ArH+NH), 5.29 (q, 1H, CH), 3.65 (dd, $^3J = 4.5$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 3.34 (dd, $^3J = 5.5$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 2.00 (s, 3H, CH_3). MS: *m/z* (%) 273 (M^+, 5.53); 230 ($M^+ - COCH_3$, 15.5), 217($M^+ - NCOCH_3$, 15.5), 162 (M^+−thenoyl, 18), 111 (thenoyl, 100). Anal. Calcd. for $C_{15}H_{15}NO_2S$ (273.35): C, 65.91; H, 5.53; N, 5.12; S, 11.73. Found: C, 65.85; H, 5.60; N, 5.10; S, 11.65%.

N-[3-Oxo-3-(thien-2-yl)-1-p-tolylpropyl]acetamide (1b)

M.p.: 118°C. $R_f = 0.26$ (PE/AcOEt 2:1). IR: ν 3295 (NH), 3080–3060 (CH, Ar), 2923–2880 (CH_3, CH_2, CH), 1662 (C=O), 1638 (CONH), 1580, 1542, 1515 (C=C, Ar) cm^{-1}. ^{1}H NMR: δ 7.84 (d, $^3J = 6.4$ Hz, 2H, ArH),

7.71 (d, $^3J = 6.4$ Hz, 2H, Ar), 7.80–7.30 (m, 4H, ArH+NH), 5.71 (q, 1H, CH), 3.76 (dd, $^3J = 4.6$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 3.34 (dd, $^3J = 5.6$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 2.29 (s, 3H, CH_3), 2.10 (s, 3H, CH_3). ^{13}C NMR: δ 192.00 (C=O), 170.32 (CONH), 145.50–127.55 (10 C_{ar}), 47.81 (CHNH), 45.43 (CH_2CO), 26.10, 21.90 (2 CH_3). MS: *m/z* (%) 287 (M^+, 4.6), 244 ($M^+ - COCH_3$, 16), 230 ($M^+ - NCOCH_3$, 30), 111 (thenoyl, 100). Anal. Calcd. for $C_{16}H_{17}NO_2S$ (287.38): C, 66.87; H, 5.96; N, 4.87; S, 11.16. Found: C, 66.83; H, 5.92; N, 4.82; S, 11.10%.

N-[1-(4-Chlorophenyl)-3-oxo-3-(thien-2-yl)propyl]acetamide (1c)

M.p.: 110°C. $R_f = 0.20$ (PE/AcOEt 2:1). IR: ν 3241 (NH), 3093–3046 (CH, Ar), 2991–2925 (CH_3, CH_2, CH), 1670 (C=O), 1649 (CONH), 1583, 1565, 1523 (C=C, Ar) cm^{-1}. ^{1}H NMR: δ 8.10 (d, $^3J = 6.6$ Hz, 2H, ArH), 7.88 (d, $^3J = 6.6$ Hz, 2H, Ar), 7.60–7.90 (m, 4H, ArH+NH), 5.80 (q, 1H, CH), 4.00 (dd, $^3J = 4.8$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.64 (dd, $^3J = 5.8$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.10 (s, 3H, CH_3). MS: *m/z* (%) 309 (M^{++2}, 3.6), 307 (M^+, 10), 264 ($M^+ - COCH_3$, 20.2), 250 ($M^+ - NCOCH_3$, 35), 182 (M^+ −thenoyl, 25), 111 (thenoyl, 100). Anal. Calcd. for $C_{15}H_{14}ClNO_2S$ (307.80): C, 58.53; H, 4.58; N, 4.55; S, 10.42. Found: C, 58.50; H,4.51; N 4.52; S, 10.40%.

N-[1-(3-Bromophenyl)-3-oxo-3-(thien-2-yl)propyl]acetamide (1d)

M.p.: 130–132°C. $R_f = 0.22$ (PE/AcOEt 2:1). IR: ν 3294 (NH), 3068–3035 (CH, Ar), 2922–2870 (CH_3, CH_2, CH), 1659 (C=O), 1646 (CONH), 1595, 1543, 1516 (C=C, Ar) cm^{-1}. ^{1}H NMR: δ 7.00–8.00 (m, 8H, ArH+NH), 5.80 (q, 1H, CH), 4.00 (dd, $^3J = 4.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.64 (dd, $^3J = 5.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.10 (s, 3H, CH_3). MS: *m/z* (%) 353 (M^{++2}, 19.6), 351 (M^+, 20), 307 ($M^+ - COCH_3$, 24), 240 (33.3), 111 (thenoyl, 100). Anal. Calcd. for $C_{15}H_{14}BrNO_2S$ (352.25): C, 51.15; H, 4.01; N, 3.98; S, 9.10. Found: C, 51.13; H, 4.00; N, 3.93; S, 9.00%.

N-[3-Oxo-1-phenyl-3-(thien-2-yl)propyl]benzamide (2a)

M.p.: 115°C. $R_f = 0.45$ (PE/AcOEt 2:1). IR: ν 3280 (NH), 3080–3030 (CH, Ar), 2922–2860 (CH_2, CH), 1658 (C=O), 1642 (CONH), 1600, 1545, 1515 (C=C, Ar) cm^{-1}. ^{1}H-NMR: δ 6.82–7.78 (m, 14H, ArH+NH), 5.29 (q, 1H, CH), 3.64 (dd, $^3J = 5$ Hz, $^2J = 16.1$ Hz, 1H, CH_2), 3.34 (dd, $^3J = 5.6$ Hz, $^2J = 16.1$ Hz, 1H, CH_2). MS: *m/z* (%) 335 (M^+, 16), 230 ($M^+ - COPh$, 25.5), 111 (thenoyl, 80), 105 (COPh, 100). Anal. Calcd. for $C_{20}H_{17}NO_2S$

(335.42): C, 71.62; H, 5.11; N, 4.18; S, 9.56. Found: C, 71.60; H, 5.80; N, 3.95; S, 9.52%.

N-[3-Oxo-3-(thien-2-yl)-1-ρ-tolylpropyl]benzamide (2b)

Mp.: 163°C. $R_f = 0.45$ (PE/AcOEt 2:1). IR: ν 3291 (NH), 3080-3060 (CH, Ar), 2923–2880 (CH_3, CH_2, CH), 1658 (C=O), 1641 (CONH), 1575, 1542, 1515 (C=C, Ar) cm^{-1}.^{1}H NMR: δ 7.78 (d, $^3J = 6.6$ Hz, 2H, ArH), 7.67 (d, $^3J = 6.6$ Hz, 2H, Ar), 7.64–7.90 (m, 9H, ArH+NH), 5.54 (q, 1H, CH), 3.76 (dd, $^3J = 4.8$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.34 (dd, $^3J = 5.6$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.30 (s, 3H, CH_3). MS: *m/z* (%) 349 (M^+, 5), 244 (M^+−COPh, 30), 111 (thenoyl, 75), 105 (COPh, 100). Anal. Calcd. for $C_{21}H_{19}NO_2S$ (349.45): C, 72.18; H, 5.48; N, 4.01; S, 9.18. Found: C, 72.13; H, 5.42; N, 4.00; S, 9.15%.

N-[1-(4-Chlorophenyl)-3-oxo-3-(thien-2-yl]propyl)benzamide (2c)

M.p. 108°C. $R_f = 0.40$ (PE/AcOEt 2:1). IR: ν 3349 (NH), 3070–3060 (CH, Ar), 2924–2853 (CH_2, CH), 1670 (C=O), 1637 (CONH), 1600, 1558, 1515 (C=C, Ar) cm^{-1}. ^{1}H NMR: δ 7.95 (d, $^3J = 6.8$ Hz, 2H, ArH), 7.78 (d, $^3J = 6.8$ Hz, 2H, Ar), 7.70–790 (m, 9H, ArH+NH), 5.85 (q, 1H, CH), 3.87 (dd, $^3J = 4.5$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.66 (dd, $^3J = 5.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2). MS: *m/z* (%) 371 (M^{++2}, 3.3), 369 (M^+, 10), 264 (M^+−COPh, 20), 250 (M^+−NCOPh, 55), 111 (thenoyl, 80), 105 (COPh, 100). Anal. Calcd. for $C_{20}H_{16}ClNO_2S$ (369.86): C, 64.95; H, 4.36; N, 3.79; S, 8.67. Found: C, 64.93; H, 4.30; N, 3.78; S, 8.62%.

N-[1-(3-Bromophenyl)-3-oxo-3-(thien-2-yl)propyl]benzamide (2d)

M.p.: 168°C. $R_f = 0.43$ (PE/AcOEt 2:1). IR: ν 3282 (NH), 3067–3030 (CH, Ar), 2922 (CH_2, CH), 1655 (C=O), 1644 (CONH), 1589, 1541, 1516 (C=C, Ar) cm^{-1}. ^{1}H NMR: δ 7.00–8.00 (m, 13H, ArH+NH), 5.80 (q, 1H, CH), 4.00 (dd, $^3J = 4.8$, $^2J = 16.3$ Hz, 1H, CH_2), 3.64 (dd, $^3J = 5.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2). MS: *m/z* (%) 414 (M^{++2}, 14.5), 413 (M^+, 15); 307 (M^+−COPh, 20), 293 (M^+−NCOPh, 50), 111 (thenoyl, 80), 105 (COPh, 100). Anal. Calcd. for $C_{20}H_{16}BrNO_2S$ (414.32): C, 57.98; H, 3.89; N, 3.38; S, 7.74. Found: C, 57.96; H, 3.85; N, 3.34; S, 7.70%.

N-[3-Oxo-1-phenyl-3-(thien-2-yl)propyl]acrylamide (3a)

M.p.: 78°C. $R_f = 0.30$ (PE/AcOEt 2:1). IR: ν 3282 (NH), 3070–3060 (CH, Ar, alkene), 2923–2854 (CH_2, CH), 1670 (C=O), 1643 (CONH), 1600, 1544, 1515 (C=C, Ar) cm^{-1}. ^{1}H NMR: δ 7.00–7.72 (m, 9H, ArH+NH), 6.32 (d, $^3J = 6.0$ Hz, 1H, CH), 6.21 (dd, $^3J = 5.4$ Hz, $^2J = 16.5$

Hz, 1H, CH_2), 5.71 (m, 1H, CH_2), 5.56 (q, 1H, CH), 3.66 (dd, $^3J = 4.8$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 3.37 (dd, $^3J = 5.7$ Hz, $^2J = 16.2$ Hz, 1H, CH_2). MS: *m/z* (%) 285 (M^+, 10), 229 ($M^+ - COCH{=}CH_2$, 90), 214 ($M^+ - NCOCH{=}CH_2$, 28), 119 (M^+-acetylthiophene, 10), 111 (thenoyl, 100), 71 ($NCOCH{=}CH_2$, 15). Anal. Calcd. for $C_{16}H_{15}NO_2S$ (285.36): C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.30; H, 5.27; N, 4.88; S, 11.22%.

N-[3-Oxo-3-(thien-2-yl)-1-ρ-tolylpropyl]acrylamide (3b)

M.p.: 88°C. $R_f = 0.32$ (PE/AcOEt 2:1). IR: ν 3290 (NH), 3090-3030 (CH_3, CH, Ar, alkene), 2923–2860 (CH_2, CH), 1660 (C=O), 1648 (CONH), 1590, 1545, 1515 (C=C, Ar) cm^{-1}. ^1H NMR: δ 7.96 (d, $^3J = 7.1$ Hz, 2H, ArH), 7.68 (d, $^3J = 7.1$ Hz, 2H, ArH), 7.66–7.90 (m, 4H, ArH+NH), 6.33 (d, $^3J = 6.0$ Hz, 1H, CH), 6.30 (dd, $^3J = 5.5$ Hz, $^2J = 16.7$ Hz, 1H, CH_2), 5.87 (m, 1H, CH_2), 5.85 (q, 1H, CH), 3.87 (dd, $^3J = 5$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.66 (dd, $^3J = 5.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.29 (s, 3H, CH_3). MS: *m/z* (%) 299 (M^+, 7), 244 ($M^+ - COCH{-}CH_2$, 90), 230 ($M^+ - NCOCH{-}CH_2$, 28), 133 (M^+ − acetylthiophene, 10), 111 (thenoyl, 100), 71 ($NCOCH{-}CH_2$, 12). Anal. Calcd. for $C_{17}H_{17}NO_2S$ (299.39): C, 68.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.17; H, 5.70; N, 4.62; S, 10.66%.

N-[1-(4-Chlorophenyl)-3-oxo-3-(thien-2-yl)propyl]acrylamide (3c)

M.p.: 165°C. $R_f = 0.22$ (PE/AcOEt 2:1). IR: ν 3250 (NH), 3090–3040 (CH, Ar, alkene), 2990–2925 (CH_3, CH_2, CH), 1675 (C=O), 1652 (CONH), 1590, 1565, 1520 (C=C, Ar) cm^{-1}. ^1H NMR: δ 8.00 (d, $^3J = 7.0$ Hz, 2H, ArH), 7.86 (d, $^3J = 7.0$, 2H, Ar), 7.00–7.85 (m, 4H, ArH+NH), 6.27 (d, d, $^3J = 6.0$ Hz, 1H, CH), 6.24 (dd, $^3J = 5.3$ Hz, $^2J = 16.5$ Hz, 1H, CH_2), 5.88 (m, 1 H, CH_2), 5.85 (q, 1H, CH), 3.88 (dd, $^3J = 4.8$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 3.69 (dd, $^3J = 5.8$ Hz, $^2J = 16.2$ Hz, 1H, CH_2). MS: *m/z* (%) 321 (M^{++2}, 1.3), 319 (M^+, 4.3), 264 ($M^+ - COCH{=}CH_2$, 29), 248 ($M^+ - NCOCH{=}CH_2$, 75), 133 (M^+ − acetylthiophene, 10), 111 (thenoyl, 100), 71 ($NCOCH{=}CH_2$, 10). Anal. Calcd. for $C_{16}H_{14}ClNO_2S$ (319.81): C, 60.09; H, 4.41; N, 4.38; S, 10.03. Found: C, 60.04; H, 4.4; N, 4.35; S, 10.00%.

N-[1-(3-Bromophenyl)-3-oxo-3-(thien-2-yl)propyl]acrylamide (3d)

M.p.: 150°C. $R_f = 0.25$ (PE/AcOEt 2:1). IR: ν 3300 (NH), 3080–3031 (CH, Ar, alkene), 2960–2925 (CH_2, CH), 1660 (C=O), 1634 (CONH), 1600, 1544, 1519 (C=C, Ar) cm^{-1}. ^1H NMR: δ 7.00–8.00 (m, 8H,

ArH+NH), 6.42 (d, $^3J = 6$ Hz, 1H, CH), 6.32 (dd, $^3J = 5.4$ Hz, $^2J = 16.5$ Hz, 1H, CH_2), 5.83 (m, 1H, CH_2), 5.81 (q, 1H, CH), 4.00 (dd, $J = 5$ Hz, 16.3 Hz, 1H, CH_2), 3.74 (dd, $J = 5.9$ Hz, 16.3 Hz, 1H, CH_2). MS: *m/z* (%) 365 ($M^{+\cdot+2}$, 9.4), 363 (M^+, 10), 307 ($M^+ - COCH{=}CH_2$, 30), 293 ($M^+ - NCOCH{=}CH_2$, 78), 189 (M^+−acetylthiophene, 10), 111 (thenoyl, 100), 71 ($NCOCH{=}CH_2$, 10). Anal. Calcd. for $C_{16}H_{14}BrNO_2S$ (364.26): C, 52.76; H, 3.87; N, 3.85; S, 8.80. Found: C, 52.74; H, 3.83; N, 3.81; S, 8.76%.

N-[3-Oxo-3-phenyl-1-(thien-2-yl)propyl]acetamide (4a)

M.p.: 90°C. $R_f = 0.25$ (PE/AcOEt 2:1). IR: ν 3310 (NH), 3060-3020 (CH, Ar), 2920–2850 (CH_3, CH_2, CH), 1670 (C=O), 1640 (CONH), 1595, 1535, 1515 (C=C, Ar) cm^{-1}. ^1H NMR: δ 6.82–7.78 (m, 9H, ArH+NH), 5.29 (q, 1H, CH), 3.75 (dd, $^3J = 4.5$ Hz, $^2J = 16.1$ Hz, 1H, CH_2), 3.44 (dd, $^3J = 5.5$ Hz, $^2J = 16.1$ Hz, 1H, CH_2), 2.00 (s, 3H, CH_3). MS: *m/z* (%) 273 (M^+, 7); 230 ($M^+ - COCH_3$, 80), 216 ($M^+ - NCOCH_3$, 28), 168 (M^+−COPh, 28), 105 (COPh, 100). Anal. Calcd. for $C_{15}H_{15}NO_2S$ (273.35): C, 65.91; H, 5.53; N, 5.12; S, 11.73. Found: C, 65.83; H, 5.61; N, 5.8; S, 11.64%.

N-[3-Oxo-1-(thien-2-yl)-3-ρ-tolylpropyl]acetamide (4b)

M.p.: 125°C. $R_f = 0.26$ (PE/AcOEt 2:1). IR: ν 3286 (NH), 3080–3060 (CH, Ar), 2920–2860 (CH_3, CH_2, CH), 1662 (C=O), 1638 (CONH), 1580, 1542, 1515 (C=C, Ar) cm^{-1}. ^1H NMR: δ 7.82 (d, $^3J = 6.5$ Hz, 2H, ArH), 7.78 (d, $^3J = 6.5$ Hz, 2H, Ar), 7.00–7.76 (m, 4H, ArH+NH), 5.71 (q, 1H, CH), 3.76 (dd, $^3J = 4.5$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 3.34 (dd, $^3J = 5.6$ Hz, $^2J = 16.2$ Hz, 1H, CH_2), 2.29 (s, 3H, CH_3), 2.10 (s, 3H, CH_3). MS: *m/z* (%) 287 (M^+, 15), 244 ($M^+ - COCH_3$, 60), 230 ($M^+ - NCOCH_3$, 20), 168 (M^+−CO-tolyl, 28), 119 (CO-tolyl, 100). Anal. Calcd. for $C_{16}H_{17}NO_2S$ (287.38): C, 66.87; H, 5.96; N, 4.87; S, 11.16. Found: C, 66.82; H, 5.91; N, 4.8; S, 11.11%.

N-[3-(4-Chlorophenyl)-3-oxo-1-(thien-2-yl)propyl]acetamide (4c)

M.p.: 115°C. $R_f = 0.20$ (PE/AcOEt 2:1). IR: ν 3246 (NH), 3090–3046 (CH, Ar), 2990–2930 (CH_2, CH), 1667 (C=O), 1644 (CONH), 1583, 1565, 1523 (C=C, Ar) cm^{-1}. ^1H NMR: δ 8.10 (d, $^3J = 6.6$ Hz, 2H, ArH), 7.88 (d, $^3J = 6.6$ Hz, 2H, Ar); 7.00-7.80 (m, 4H, ArH+NH), 5.80 (q, 1H, CH), 3.82 (dd, $^3J = 4.5$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.54 (dd, $^3J = 5.8$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.12 (s, 3H, CH_3). ^{13}C-NMR: δ 197.00 (C=O), 169.32 (CONH), 144.27-124.57 (10 C_{ar}), 45.80 (CHNH), 43.43 (CH_2CO), 23.36 ($COCH_3$). MS: *m/z* (%) 309 ($M^{+\cdot+2}$, 3.6), 307 (M^+, 10), 264 ($M^+ - COCH_3$,

20), 249 ($M^+-NCOCH_3$, 65), 139 (4-ClC_6H_4-CO, 100). Anal. Calcd. for $C_{15}H_{14}ClNO_2S$ (307.80): C, 58.53; H, 4.58; N, 4.55; S, 10.42. Found: C, 58.52; H, 4.50; N, 4.5; S, 10.42%.

N-(3-(4-Bromophenyl)-3-oxo-1-(thien-2-yl)propyl)acetamide (4d)

M.p.: 136°C. $R_f = 0.22$ (PE/AcOEt 2:1). IR: ν 3268 (NH), 3090–3060 (CH, Ar), 2940–2880 (CH_3, CH_2, CH), 1669 (C=O), 1643 (CONH), 1580, 1542, 1519 (C=C, Ar) cm^{-1}. ^1H NMR: δ 8.20 (d, $^3J = 6.6$ Hz, 2H, ArH), 7.95 (d, $^3J = 6.6$ Hz, 2H, Ar), 7.00–7.60 (m, 4H, ArH+NH), 5,88 (q, 1H, CH), 3.88 (dd, $^3J = 5$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.64 (dd, $^3J = 5.8$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.1 (s, 3H, CH_3). MS: *m/z* (%) 353 (M^{++2}, 19.6), 351 (M^+, 20), 307 (M^+-COCH_3, 30), 294 ($M^+-NCOCH_3$, 80), 182 (4-Br-C_6H_4-CO, 100). Anal. Calcd. for $C_{15}H_{14}BrNO_2S$ (352.25): C, 51.15; H, 4.01; N, 3.98; S, 9.10. Found: C, 51.11; H, 4.0; N, 3.92; S, 88%.

N-[3-Oxo-3-phenyl-1-(thien-2-yl)propyl]benzamide (5a)

M.p.: 110°C. $R_f = 0.45$ (PE/AcOEt 2:1). IR: ν 3282 (NH), 3080–3020 (CH, Ar), 2925 (CH_2, CH), 1659 (C=O), 1646 (CONH), 1600, 1545, 1515 (C=C, Ar) cm^{-1}. ^1H NMR: δ 6.88–7.78 (m, 14H, ArH+NH), 5.29 (q, 1H, CH); 3.62 (dd, $^3J = 4.5$ Hz, $^2J = 16.1$ Hz, 1H, CH_2), 3.46 (dd, $^3J = 5.6$ Hz, $^2J = 16.1$ Hz, 1H, CH_2). MS: *m/z* (%) 335 (M^+, 4.22); 230 (M^+-COPh, 33.3), 116 (NCOPh, 75), 105 (COPh, 100). Anal. Calcd. for $C_{20}H_{17}NO_2S$ (335.42): C, 71.62; H, 5.11; N, 4.18; S, 9.56. Found: C, 71.61; H, 5.81; N, 3.96; S, 9.53%.

N-[3-Oxo-1-(thien-2-yl)-3-ρ-tolylpropyl]benzamide (5b)

M.p.: 150°C. $R_f = 0.46$ (PE/AcOEt 2:1). IR: ν 3291 (NH), 3080–3060 (CH, Ar), 2923–2880 (CH_3, CH_2, CH), 1660 (C=O), 1642 (CONH), 1575, 1542, 1515 (C=C, Ar) cm^{-1}. ^1H NMR: δ 7.75 (d, $^3J = 6.6$ Hz, 2H, ArH), 7.67 (d, $^3J = 6.6$ Hz, 2H, Ar), 7.00–7.80 (m, 9H, ArH+NH), 5.58 (q, 1H, CH), 3.79 (dd, $^3J = 4.8$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.38 (dd, $^3J = 5.6$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.30 (s, 3H, CH_3). MS: *m/z* (%) 349 (M^+, 8.2), 244 (M^+-COPh, 33.3), 230 ($M^+-COtolyl$, 43.3), 119 (COtolyl, 100), 105 (COPh, 90). Anal. Calcd. for $C_{21}H_{19}NO_2S$ (349.45): C, 72.18; H, 5.48; N, 4.01; S, 9.18. Found: C, 72.14; H, 5.40; N, 4.0; S, 9.14%.

N-[3-(4-Chlorophenyl)-3-oxo-1-(thien-2-yl)propyl]benzamide (5c)

M.p.: 120°C. $R_f = 0.40$ (PE/AcOEt 2:1). IR: ν 3350 (NH), 3070–3060 (CH, Ar), 2924–2853 (CH_3, CH_2, CH), 1675 (C=O), 1635 (CONH), 1600, 1558, 1515 (C=C, Ar) cm^{-1}. ^1H-NMR: δ 8.00 (d, $^3J = 6.8$ Hz, 2H, ArH),

7.90 (d, $^3J = 6.8$ Hz, 2H, Ar), 7.00–7.85 (m, 9H, ArH+NH), 5.88 (q, 1H, CH), 3.98 (dd, $^3J = 4.6$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.76 (dd, $^3J = 5.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2). MS: m/z (%) 371 (M^+, 2.6), 369 (M^+, 8), 264 (M^+−COPh, 65), 230 (M^+−4-Cl-C_6H_4-CO), 139 (4-Cl-C_6H_4, 50), 105 (COPh, 100). Anal. Calcd. for $C_{20}H_{16}ClNO_2S$ (369.86): C, 64.95; H, 4.36; N, 3.79; S, 8.67. Found: C, 64.92; H, 4.32; N, 3.77; S, 8.6%.

N-[3-(4-Bromophenyl)-3-oxo-1-(thien-2-yl)propyl]benzamide (5d)

M.p.: 168°C. $R_f = 0.43$ (PE/AcOEt 2:1). IR: ν 3290 (NH), 3070–3030 (CH, Ar), 2922 (CH_2, CH), 1655 (C=O), 1644 (CONH), 1580, 1541, 1516 (C=C, Ar) cm^{-1}. ^1H NMR: δ 8.10 (d, $^3J = 6.8$ Hz, 2H, ArH), 7.95 (d, $^3J = 6.8$ Hz, 2H, Ar), 7.00-7.85 (m, 9H, ArH+NH), 5.88 (q, 1H, CH), 3.98 (dd, $^3J = 4.5$ Hz, ^2J=16.3 Hz, 1H, CH_2), 3.76 (dd, $^3J = 5.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2). MS: *m/z* (%) 415 (M^{++2}, 9.9), 413 (M^+, 10), 307 (M^+−COPh, 75), 230 (M^+−4-Br-C_6H_4, 8), 182 (4-Br-C_6H_4-CO, 60), 105 (COPh, 100). Anal. Calcd. for $C_{20}H_{16}BrNO_2S$ (414.32): C, 57.98; H, 3.89; N, 3.38; S, 7.74. Found: C, 57.94; H, 3.84; N, 3.33; S, 7.71%.

N-[3-Oxo-3-phenyl-1-(thien-2-yl)propyl]acrylamide (6a)

M.p. 64°C. $R_f = 0.30$ (PE/AcOEt 2:1). IR: ν 3282 (NH), 3070–3060 (CH, Ar, alkene), 2923–2854 (CH_2, CH), 1670 (C=O), 1643 (CONH), 1600, 1544, 1515 (C=C, Ar) cm^{-1}. ^1H NMR: δ 6.89–7.74 (m, 9H, ArH+NH), 6.24 (d, $^3J = 6.0$ Hz, 1H, CH), 6.21 (dd, $^3J = 5.3$ Hz, $^2J = 16.5$ Hz, 1H, CH_2), 5.59 (m, 1H, CH_2), 5.56 (q, 1H, CH), 3.66 (dd, $^3J = 4.8$ Hz, 16.2 Hz, 1H), 3.37 (dd, $^3J = 5.7$ Hz, $^2J = 16.2$ Hz, 1H, CH_2). MS: *m/z* (%) 285 (M^+, 10), 229 (M^+ −COCH=CH_2, 85), 216 (M^+ −NCOCH=CH_2, 38), 105 (COPh, 100), 71 (N COCH=CH_2, 12). Anal. Calcd. for $C_{16}H_{15}NO_2S$ (285.36): C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.32; H, 5.29; N, 4.9; S, 11.21%.

N-[3-Oxo-1-(thien-2-yl)-3-ρ-tolylpropyl]acrylamide (6b)

M.p.: 105°C. $R_f = 0.31$ (PE/AcOEt 2:1). IR: ν 3293 (NH), 3090–3030 (CH, Ar, alkene), 2925–2860 (CH_2, CH), 1660 (C=O), 1648 (CONH), 1595, 1545, 1515 (C=C, Ar) cm^{-1}. ^1H NMR: δ 7.99 (d, $^3J = 7.1$ Hz, 2H, ArH), 7.87 (d, $^3J = 7.1$ Hz, 2H, Ar), 7.00–7.80 (m, 4H, ArH+NH), 6.31 (d, $^3J = 6.0$ Hz, 1H, CH), 6.20 (dd, $^3J = 5.4$ Hz, $^2J = 16.5$ Hz, 1H, CH_2), 5.88 (m, 1H, CH_2), 5.85 (q, 1H, CH), 3.87 (dd, $^3J = 4.6$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 3.66 (dd, $^3J = 5.7$ Hz, $^2J = 16.3$ Hz, 1H, CH_2), 2.29 (s, 3H, CH_3). MS: *m/z* (%) 299 (M^+, 4.4), 244 (M^+ −COCH=CH_2, 75), 230 (M^+ −NCOCH=CH_2, 48), 119 (COtolyl, 100), 71 (N COCH=CH_2, 12). Anal.

Calcd. for $C_{17}H_{17}NO_2S$ (299.39): C, 68.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.18; H, 5.72; N, 4.63; S, 10.68%.

N-[3-(4-Chlorophenyl)-3-oxo-1-(thien-2-yl)propyl]acrylamide (6c)

M.p.: 130°C. $R_f = 0.22$ (PE/AcOEt 2:1). IR: ν 3303 (NH), 3060, 3031(CH, Ar, alkene), 2900 (CH_2, CH), 1685 (C=O), 1636 (CONH), 1600, 1544, 1519 (C=C, Ar) cm^{-1}. ^1H NMR: δ 8.20 (d, $^3J = 7.0$ Hz, 2H, ArH), 7.96 (d, $^3J = 7.0$ Hz, 2H, Ar), 7.90–7.30 (m, 4H, ArH+NH), 6.34 (d, $^3J = 6.0$ Hz, 1H, CH), 6.32 (dd, $^3J = 5.5$ Hz, $^2J = 16.7$ Hz, 1H, CH_2), 5.87 (m, 1H, CH_2), 5.85 (q, 1H, CH), 3.95 (dd, $^3J = 4.6$ Hz, $^2J = 16.2$ Hz, 1H CH_2), 3.79 (dd, $^3J = 5.8$ Hz, $^2J = 16.2$ Hz, 1H, CH_2). MS: *m/z* (%) 321 (M^{++2}, 3.6), 319 (M^+, 10), 264 ($M^+ - COCH{=}CH_2$, 74.3), 250 ($M^+ - NCOCH{=}CH_2$, 45), 180 ($M^+ - 4\text{-Cl-}C_6H_4$, 5.4), 139 (4-Cl-C_6H_4-CO^+, 100). Anal. Calcd. for $C_{16}H_{14}ClNO_2S$ (319.81): C, 60.09; H, 4.41; N, 4.38; S, 10.03. Found: C, 60.06; H, 4.38; N, 4.36; S, 10.01%.

N-[3-(4-Bromophenyl)-3-oxo-1-(thien-2-yl)propyl]acrylamide (6d)

M.p.: 162°C. $R_f = 0.26$ (PE/AcOEt 2:1). IR: ν 3297 (NH), 3080–3031 (CH, Ar, alkene), 2956–2925 (CH_2, CH), 1660 (C=O), 1634 (CONH), 1600, 1544, 1519 (C=C, Ar) cm^{-1}. ^1H NMR: δ 8.20 (d, $^3J = 6.9$ Hz, 2H, ArH), 7.95 (d, $^3J = 6.9$ Hz, 2H, Ar), 7.00-7.81 (m, 4H, ArH+NH), 6.40 (d, $^3J = 6.0$ Hz, 1H, CH), 6.31 (dd, $^3J = 5.4$ Hz, $^2J = 16.5$ Hz, 1H, CH_2), 5.40 (m, 1H, CH_2), 5.88 (q, 1H, CH), 3.88 (dd, $^3J = 4.8$ Hz, $^2J = 16.1$ Hz, 1H, CH_2), 3.66 (dd, $^3J = 5.8$ Hz, $^2J = 16.1$ Hz, 1H, CH_2). MS: *m/z* (%) 365 (M^{++2}, 17.6), 363 (M^+, 18), 307 ($M^+ - COCH{=}CH_2$, 84.3), 294 ($M^+ - NCOCH{=}CH_2$, 38), 183 (4-Br-C_6H_4-CO, 100). Anal. Calcd. for $C_{16}H_{14}BrNO_2S$ (364.26): C, 52.76; H, 3.87; N, 3.85; S, 8.80. Found: C, 52.73; H, 3.85; N, 3.82; S, 8.79%.

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