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Oxidative desulfurization of disubstituted thioureas using Pb(II) salts and investigation of pK_a-dependent regioselective N-acylation

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A highly efficient method for the N-acylation of both symmetrical and unsymmetrical thioureas by the use of lead (II) salts and triethylamine has been achieved. The reaction gives regioselective *N*-acylated product for unsymmetrical thiourea. For unsymmetrical thiuourea, regioselective N-acylation takes place towards the amine having lower pK_a. A linear correlation between the pK_as of the amines and the regioselective N-acylation is found. Another attractive feature of this transformation is that lead sulfide, which is important to material science, is obtained as a side product (nanocubes of 20 nm).

Keywords: thiourea; desulfurization; N-acylation; urea; regioselective

1. Introduction

For the construction of heterocycles, ureas and thioureas are very useful synthons (*1*). *N*-Acylureas have found diverse application in agrochemicals and pharmaceuticals (*2*). For example, derivatives of acylurea have been used for various synthetic methodologies (*3a–i*). The anti-Parkinson agent cabergoline is an *N*-acyl urea derivative (*4*). *N*-Acylated products can additionally be employed as interesting semi-crystalline materials and auxiliaries for the preparation of chiral cyclic carboxylic acids (*5*). On the other hand, lead compounds have found diverse application in organic transformations despite their associated toxicity, and their application has dominated the field of material science in recent years. Lead sulphide (PbS) nanomaterials, due to their narrow band gap (0.4–0.9 eV), are semiconductors that possess special optoelectronic properties, which have a diverse array of application (*6*). A number of PbS nanomaterials with different morphologies and structures, such as nanobelts (*7*), nanoparticles (*8*), nanorods (*9*), nanowires (*10*), nanoflakes (*11*) and nanocubes (*12*), have been synthesized.

N-Acylated ureas can be generated from the corresponding thioureas by several methods. N-Acylation has been achieved from ureas using acetyl chloride or acids at elevated temperatures, the reaction of amides with isocyanates or carbodiimides with acids (*13*). Recently, regioselective

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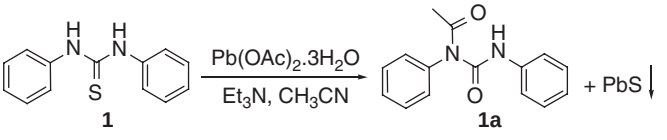
N-acetylation of asymmetrical ureas bearing aryl and alkyl groups has been achieved using $Mn(OAc)_3$ (*14*). Our group has also recently reported an efficient method for the regioselective N-acylation of symmetrical and unsymmetrical ureas using diacetoxyiodobenzene (DIB) (*15*). The high cost of the DIB is the main detraction of its use, which ultimately inspired us to explore a more cost-effective route to these compounds.

2. Results and discussion

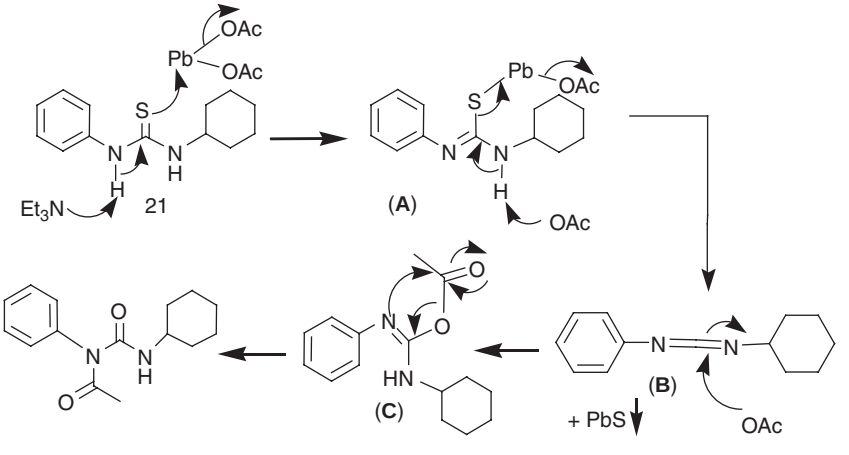
Manganese and hypervalent iodine-based reagents are thiophilic in nature and so are lead compounds. This prompted us to investigate whether lead acetate could serve as an *N*-acylating agent for the N-acylation of thioureas. The other objective was to find out the origin of regioselectivity in the *N*-acylation of unsymmetrical thioureas. In this article, we have demonstrated an unprecedented regioselective N-acetylation of 1,3-disubstituted thioureas leading to *N*-acetyl ureas with concurrent formation of PbS nanomaterials using $Pb(OAc)_2 \cdot 3H_2O$ (Scheme 1).

In a typical reaction, one equivalent of 1,3-diphenylthiourea **1**, one equivalent of $Pb(OAc)_2 \cdot 3H_2O$ and two equivalents of triethylamine were mixed together in acetonitrile and stirred at room temperature. Complete conversion was observed after 12 h; however, when the reaction was performed at elevated temperature (60 °C) complete conversion was achieved within 2 h. Progress of the reaction was observed by the appearance of the black colored precipitate of PbS. The proposed mechanism for the formation of *N*-acetylated product is shown in Scheme 2.

Formation of the *N*-acylated product, along with PbS as the byproduct, can be explained with the help of the mechanism shown in Scheme 2. The sulfur atom of the 1,3-disubstituted thiourea attacks the thiophilic center Pb(II) of $Pb(OAc)_2$, displacing one of the acetate groups and affording the intermediate (**A**). The proton abstraction by triethylamine is from the phenyl side of the



Scheme 1. N-Acylation of urea and formation of PbS nanocrystallite.



Scheme 2. Proposed mechanism of formation of *N*-acylurea.

1,3-disubstituted thiourea (**21**), as the pK_a of the parent amine aniline (pK_a 4.63) attached to one side of the thiourea is lower in comparison to the cyclohexylamine (pK_a 10.66) attached to the other side (*16*). Reductive β-elimination of intermediate **A** with the expulsion of PbS produces carbodiimide intermediate **B**. The formation of carbodiimide has been confirmed by recording the IR spectrum of the crude reaction mixture at approximately 50% conversion (as judged by TLC).

The size and shapes of PbS particles were examined using TEM. The shape of the PbS crystallite was found to be nanocube (Figure 1), and the size was approximately 20 nm.

After formulating a plausible reaction mechanism, we focussed our attention on the scope of this N-acylation reaction on various thioureas. Symmetrical thioureas **2** and **3** afforded their corresponding mono-acylated product in moderate to good yields (Table 1). When an *o*-disubstituted thiourea, as in the case of **4**, was reacted under identical reaction conditions, no traces of acetylated product were observed. This is probably due to the steric crowding of the two *o*-methyl groups. Other 1,3-diaryl thioureas **5**, **6**, **7** and **8** gave their corresponding acylated product in good yields. When the methodology was applied to 1,3-cyclohexyl thiourea **9**, no traces of acetylated product could be detected. This is possibly due to the higher pK_a of the cyclohexyl amine compared with aryl amines (*16*). As such, the triethylamine base used (pK_a 10.78) was not basic enough to abstract a proton from the cyclohexyl amine (pK_a 10.66) of thiourea **9** as demanded by the mechanism.

Having successfully synthesized a series of *N*-acylated ureas, we were interested in exploring the regioselective N-acylation of unsymmetrical thioureas. The larger the difference between the pK_as of the precursor amines in the thioureas, the higher the regioselectivity of N-acylation observed, with preferential acylation taking place toward the amine possessing the lower pK_a. The attack of the acetate group to an unsymmetrical carbodiimide would lead to the protonation toward the amine/imine having more basic character (higher pK_a), while not affecting the imine group on the other side. The resultant isourea, as proposed in Scheme 2, would then lead to the formation of *N*-acylated product after rearrangement.

The measured pK_as of aniline and *p*-methyl aniline are 4.63 and 5.08, respectively (*16*). For unsymmetrical thiourea **10**, *p*-methyl aniline nitrogen is more basic compared with aniline nitrogen of the carbodiimide intermediate; thus, the former is acylated (40%) compared with the later (60%) as evident from the ^{1}H NMR.

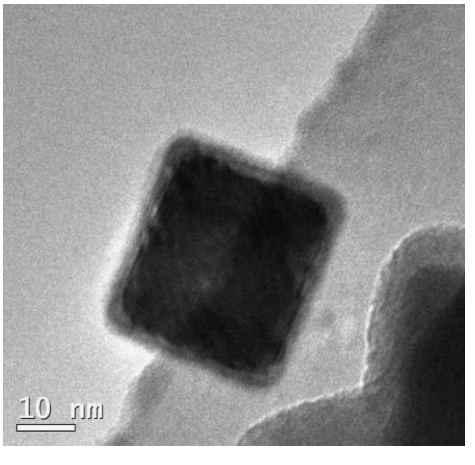
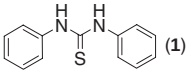
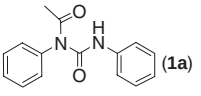
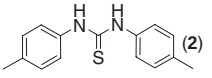
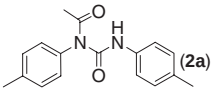
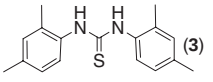
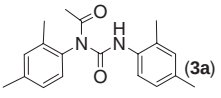
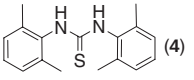
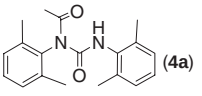
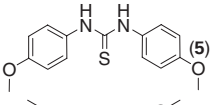
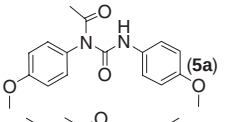
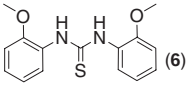
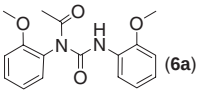
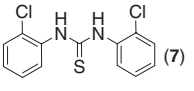
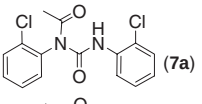
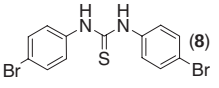
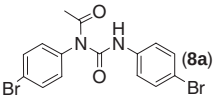
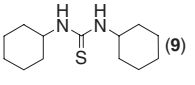
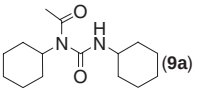


Figure 1. TEM picture of nanocubical PbS.

Table 1. N-Acylation of ureas from symmetrical thiourea.

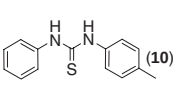
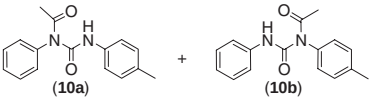
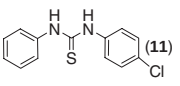
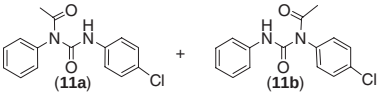
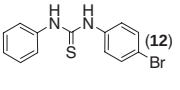
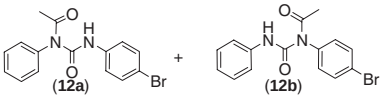
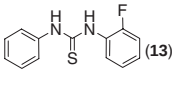
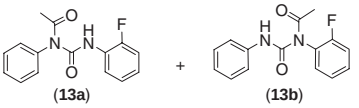
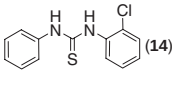
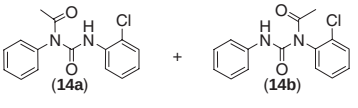
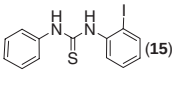
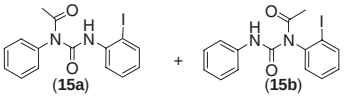
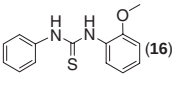
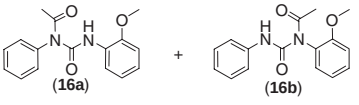
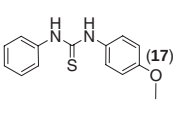
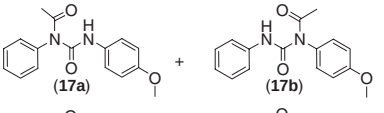
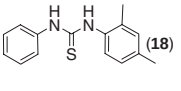
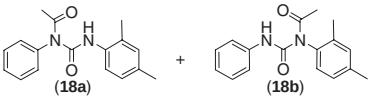
Substrate	Product	Yield %
 (**1**)	 (**1a**)	78
 (**2**)	 (**2a**)	81
 (**3**)	 (**3a**)	69
 (**4**)	 (**4a**)	0
 (**5**)	 (**5a**)	86
 (**6**)	 (**6a**)	83
 (**7**)	 (**7a**)	83
 (**8**)	 (**8a**)	52
 (**9**)	 (**9a**)	0

Notes: Reactions were monitored by TLC. Products were confirmed by IR, ^{1}H NMR and ^{13}C NMR and the yield is isolated yield.

To support our arguments that regioselectivity is largely dependent on the pK_as of the amine, acylation of number of unsymmetrical thioureas was performed (Table 2). The measured pK_as of *p*-chloro (pK_a 4.15), *p*-bromo (pK_a 3.86), *o*-fluoro (pK_a 3.20), *o*-chloro (pK_a 2.65), *o*-iodo (pK_a 2.60) and *o*-methoxy (pK_a 4.52) anilines are lower than that of aniline (pK_a 4.63) (*16*); thus, the preferential N-acylation took place toward the *p*-chloro, *p*-bromo, *o*-fluoro, *o*-chloro, *o*-iodo and *o*-methoxy aniline sides in substrates **11**, **12**, **13**, **14**, **15** and **16**, giving major products **11b**, **12b**, **13b**, **14b**, **15b** and **16b**, respectively. In substrates **17** and **18** possessing *p*-methoxy and 2,4-dimethyl aniline, the measured pK_as of the parent amines are 5.34 and 4.88, respectively (*16*). These values are higher when compared with aniline; thus, preferential acylation took place toward these amines to afford regioselective products **17a** and **18a**, respectively. We found that the larger the difference between the pK_as of the amine attached to the thiourea, the greater the regioselectivity observed.

The pK_a difference and the ratio of regioselectivity are tabulated in Table 3 and shown graphically in Figure 2. The ratios of regioselectivities were calculated assuming the N-acylation toward

Table 2. Regioselective N-acylation of ureas from thioureas.

Substrate	Product[b]	Yield % / Ratio
 (**10**)	 (**10a**) + (**10b**)	82 (60 : 40)
 (**11**)	 (**11a**) + (**11b**)	86 (34 : 66)
 (**12**)	 (**12a**) + (**12b**)	85 (32 : 68)
 (**13**)	 (**13a**) + (**13b**)	78 (20 : 80)
 (**14**)	 (**14a**) + (**14b**)	79 (19 : 81)
 (**15**)	 (**15a**) + (**15b**)	70 (32 : 68)
 (**16**)	 (**16a**) + (**16b**)	75 (43 : 57)
 (**17**)	 (**17a**) + (**17b**)	75 (55 : 45)
 (**18**)	 (**18a**) + (**18b**)	91 (73 : 27)

Notes: Reactions were monitored by TLC. Products were confirmed by IR, ^{1}H NMR and ^{13}C NMR and the ratio was determined by ^{1}H NMR.

the aniline nitrogen side as unity and the other side as the ratio of it. A plot of pK_a difference of various substituted aromatic amines with respect to aniline in the *x*-axis and regioselectivity in the *y*-axis shows a linear relationship for most of the substrates examined. A negative value of pK_a difference means the ratio of regioselectivity is less than one and positive value means more than one (Table 3). A direct correlation between the pK_a difference and regioselectivity should fall on a straight line. From the graph (Figure 2), there seems to be few deviations in cases of **13**, **15** and **18** having fluoro, iodo and methyl groups in the *o*-position. These deviations may be due to the steric factors of these substituents.

Although the pK_a difference between the 2,6-dimethyl aniline (pK_a 4.74) and aniline (pK_a 4.61) in substrate **19** is small, it gave exclusively regioselective product **19a** instead of a mixture of products. This is presumably due to the steric factor imparted by the two *o*-substituted methyl groups. Again, the higher acidic character of the aromatic amine aniline (pK_a 4.61) and

Table 3. Regioselective N-acylation of ureas as a function of pK_a (*16*).

Thioureas	pK_{a1}–pK_{a2}	Ratio of regioselectivity
10	(−) 0.45	1 : 0.66
11	(+) 0.48	1 : 1.94
12	(+) 0.77	1 : 2.12
13	(+) 1.43	1 : 4.00
14	(+) 1.98	1 : 4.26
15	(+) 2.03	1 : 2.13
16	(+) 0.11	1 : 1.32
17	(−) 0.71	1 : 0.81
18	(−) 0.25	1 : 0.36

Notes: pK_{a1} = pK_a of aniline, pK_{a2} = pK_a of other amine attached to thiourea.

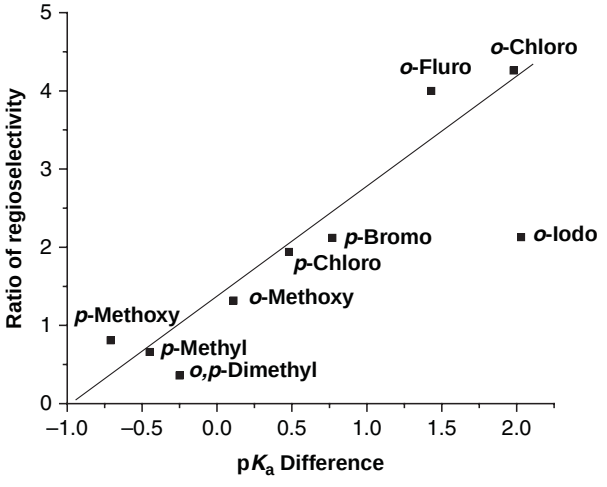
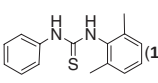
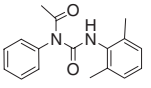
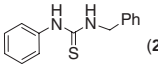
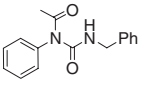
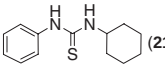
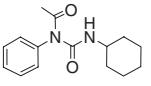
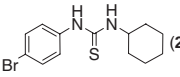
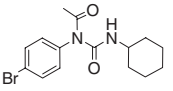


Figure 2. Plot of pK_a-dependent regioselectivity.

p-bromoaniline (pK_a 3.86) compared with aliphatic amines, such as benzylamine (pK_a 9.41) and cyclohexylamine (pK_a 10.66), indicates that the acylation is toward the aniline and *p*-bromoaniline side of the urea, as shown for substrates **20**–**22** (Table 4). Thus, the exclusive regioselective formation of products **20a**, **21a** and **22a** appears to be due to the large difference in their pK_as.

After investigating the regioselectivity, we were interested in developing a general method for the preparation of various other *N*-acylated ureas form 1,3-disubstituted thioureas. We envisioned that this could be achieved by two different strategies. In the first strategy, an external acid can be added in large excess so that it can attack on carbodiimide to give the *N*-acylated product. This method, while successful, invariably formed *N*-acetylated product along with the desired *N*-acylated product. This reaction goes via carbodiimide intermediate that is attacked by a nucleophilic acetate anion released from $Pb(OAc)_2$. Thus, in an alternative method, the possible replacement of the lead salt with a non-nucleophilic counter ion, such as nitrate or chloride, and supplying the acetate ion/acid externally would form *N*-acylated ureas. Two lead salts, $PbCl_2$ and $Pb(NO_3)_2$ (Table 5), were tested for this purpose, and the latter was found to be more efficient. In this strategy, when 1,3-diphenylthiourea (1 equivalent), $Pb(NO_3)_2$ (1.5 equivalent), triethylamine (4 equivalent) and acid (2.5 equivalent) were mixed together in acetonitrile and stirred at an elevated temperature (80 °C), complete conversion was achieved within 1 h. The proposed

Table 4. Regioselective N-acylation of ureas from thiourea.

Substrate	Product	Yield %
 (**19**)	 (**19a**)	82
 (**20**)	 (**20a**)	65
 (**21**)	 (**21a**)	70
 (**22**)	 (**22a**)	70

Notes: Reactions were monitored by TLC. Products were confirmed by IR, ^{1}H NMR and ^{13}C NMR.

mechanism for the formation of *N*-acylated product is presumably similar to that stated earlier. Here, the added acid attacks the carbodiimide intermediate to afford the *N*-acylated product.

3. Conclusion

In conclusion, we have reported an efficient method for the synthesis of *N*-acylated ureas from 1,3-disubstituted thioureas using $Pb(OAc)_2 \cdot 3H_2O$ or $Pb(NO_3)_2$. For the first time, $Pb(OAc)_2 \cdot 3H_2O$ has been employed as an acylating agent. We have found a direct correlation between the regioselectivity and the pK_as of the amines: the larger the pK_a difference between the amines, the greater the regioselectivity observed. The concurrent formation of PbS nanocrystallite is also an attractive feature of this methodology.

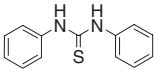
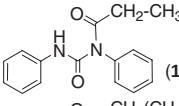
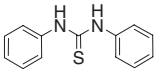
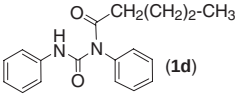
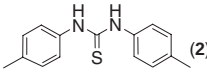
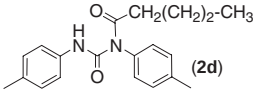
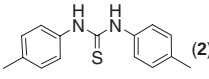
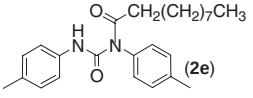
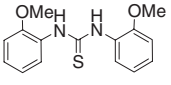
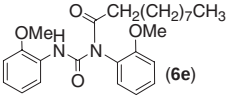
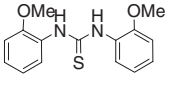
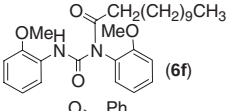
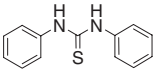
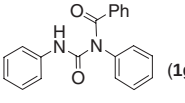
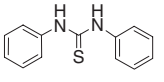
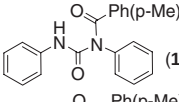
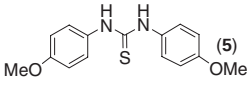
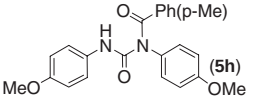
4. Experimental

All the reagents were of commercial grade and purified according to established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). Column chromatography was performed using silica gel (60–120 mesh). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz); the chemical shifts are expressed as δ values (ppm). HRMS spectra were recorded using WATERS MS system, Q-Tof premier and data analysed using Mass Lynx 4.1. Melting points were recorded in a Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

4.1. *General procedure for the preparation of N-acylated urea (1a) from thiourea (1)*

To a stirred solution of diphenylthiourea **1** (228 mg, 1 mmol) and triethylamine (276 µl, 2 mmol) in acetonitrile (5 ml), lead acetate trihydrate (379 mg, 1 mmol) was added and the reaction mixture was heated at 60 °C for 2 h. A black colored precipitate of PbS was observed during this period.

Table 5. N-Acylation of ureas from thiourea using $Pb(NO_3)_2$ various acids.

Substrate	Acid	Product	Yield %
 (**1**)	CH_3CH_2COOH	 (**1c**)	66
 (**1**)	$CH_3(CH_2)_3COOH$	 (**1d**)	62
 (**2**)	$CH_3(CH_2)_3COOH$	 (**2d**)	65
 (**2**)	$CH_3(CH_2)_8COOH$	 (**2e**)	63
 (**6**)	$CH_3(CH_2)_8COOH$	 (**6e**)	73
 (**6**)	$CH_3(CH_2)_{10}COOH$	 (**6f**)	71
 (**1**)	PhCOOH	 (**1g**)	65
 (**1**)	(p-Me)PhCOOH	 (**1h**)	66
 (**5**)	(p-Me)PhCOOH	 (**5h**)	63

Notes: Reactions were monitored by TLC. Products were confirmed by IR, ^{1}H NMR and ^{13}C NMR.

The precipitated PbS was filtered, the organic layer evaporated and the resulting residue was mixed with ethyl acetate (15 ml). The ethyl acetate layer was washed with water (3×5 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product **1a**. Compound **1a** was recrystallized from a mixture of ethyl acetate:hexane (8:2) to afford colorless crystals.

4.2. *General procedure for the preparation of N-acylurea (1d) from thiourea (1) and pentanoic acid*

To a stirred solution of diphenylthiourea **1** (228 mg, 1 mmol), triethylamine (552 μL, 4 mmol) and pentanoic acid (255 mg, 2.5 mmol) in acetonitrile (5 ml), lead nitrate (331 mg, 1.5 mmol) was added, and the reaction mixture was heated at 80 °C for 1 h. A black colored precipitate of PbS was observed during this period. The precipitated PbS was filtered hot and washed with acetonitrile (2×2 ml). The organic layer was evaporated, and the resulting residue was mixed with ethyl

Table 6. Spectral and analytical data.

Entry	Spectral data
1a (*15*)	m.p. 100–102 °C; ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 3H, CH_3), 7.08 (t, 1H, $J = 7.2$ Hz, Ar−H), 7.28 (m, 4H, Ar−H), 7.48 (m, 5H, Ar−H), 11.44 (br s, 1H, NH). ^{13}C NMR($CDCl_3$): δ 26.8, 120.3, 124.3, 129.1, 129.2, 129.3, 129.9, 137.8, 139.0, 152.1 (NH−C=O), 175.2 (C=O). IR (KBr): 3230 (m), 2857 (w), 1722 (s), 1668 (m), 1602 (m) cm^{-1}. HRMS (ESI): MH$^+$, found 255.2946, $C_{15}H_{15}N_2O_2$ requires 255.2957.
6a	m.p. 149–151 °C; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 4.05 (s, 3H, CH_3), 4.17 (s, 3H, CH_3), 7.08–7.14 (m, 2H, Ar−H), 7.20–7.30 (m, 3H, Ar−H), 7.45 (m, 1H, Ar−H), 7.63 (m, 1H, Ar−H), 8.47 (m, 1H, Ar−H), 11.99 (brs, 1H, NH). ^{13}C NMR($CDCl_3$): δ 25.6, 55.8, 56.0, 110.1, 112.1, 119.9, 121.0, 121.2, 123.5, 127.7, 128.0, 130.4, 130.7, 148.7, 151.4, 155.3 (NH−C=O), 175.3 (C=O). IR (KBr): 3133 (w), 1719 (s), 1672 (w), 1531 (m) cm^{-1}. HRMS (ESI): MH$^+$, found 315.1328, $C_{17}H_{18}N_2O_4$ requires 315.3481.
22a	m.p. 104–106 °C; ^{1}H NMR ($CDCl_3$): δ 1.32 (m, 6H), 1.60 (m, 1H), 1.71 (m, 2H), 1.92 (s, 3H), 1.95 (m, 1H), 3.70 (m, 1H), 7.11 (d, 2H, $J = 8.4$ Hz, Ar−H), 7.58 (d, 2H, $J = 8.4$ Hz, Ar−H), 9.04 (d, 1H, $J = 6$ Hz, Ar−H). ^{13}CNMR ($CDCl_3$): δ 24.8, 25.7, 26.6, 33.0, 49.6, 122.9, 131.0, 132.9, 138.6, 153.5 (NH−C=O), 174.1 (C=O). IR (KBr): 3316 (w), 1705 (s), 1664 (w), 1510 (m) cm^{-1}. $C_{15}H_{19}BrN_2O_2$ (339.23): calcd. C 53.11%, H 5.65%, N 8.26%; found: C 53.14%, H 5.66%, N 8.23%.
1d	m.p. 73–75 °C; ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H, $J = 7.2$ Hz, CH_3), 1.23 (m, 2H, CH_2), 1.56 (m, 2H, CH_2), 2.14 (t, 2H, $J = 7.2$ Hz, CH_2), 7.08 (t, 1H, $J = 7.2$ Hz, Ar−H)), 7.24–7.32 (m, 4H, Ar−H), 7.44–7.54 (m, 3H, Ar−H), 7.55 (m, 2H, Ar−H), 11.56 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.9, 22.2, 26.8, 37.6, 120.3, 124.2, 129.1, 129.2, 129.4, 129.9, 137.9, 138.4, 152.3 (NH−C=O), 177.8 (C=O). IR (KBr): 3131 (w), 2957 (w), 1721 (s), 1660 (w),1562 (m) cm^{-1}. $C_{18}H_{20}N_2O_2$ (296.37): calcd. C 72.95%, H 6.80%, N 9.45%; found: C 72.98%, H 6.72%, N 9.42%.
2d	m.p. 106–108 °C; ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H, $J = 7.2$ Hz, CH_3), 1.24 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 2.16 (t, 2H, $J = 7.6$ Hz, CH_2), 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.11 (m, 4H, Ar−H), 7.27 (d, 2H, $J = 8.0$ Hz, Ar−H), 7.43 (d, 2H, $J = 8.0$ Hz, Ar−H), 11.47 (br s, 1H, NH). ^{13}CNMR (100 MHz, $CDCl_3$): δ 13.9, 20.9, 21.4, 22.2, 26.8, 37.5, 120.2, 129.0, 129.6, 130.5, 133.6, 135.4, 135.8, 139.1, 152.3 (NHC=O), 177.9 (C=O). IR (KBr): 175 (w), 2959 (m), 1715 (s), 1591 (m) cm^{-1}. $C_{20}H_{24}N_2O_2$ (324.43): calcd. C 74.05%, H 7.46%, N 8.63%; found: C 74.13%, H 7.42%, N 8.60%.
2e	m.p. 86–88 °C; g^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, $J = 7.6$ Hz, CH_3), 1.22 (m, 12H, 6CH_2), 1.56 (m, 2H, CH_2), 2.15 (t, 2H, $J = 7.2$ Hz, CH_2), 2.30 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.11 (m, 4H, Ar−H), 7.27 (d, 2H, $J = 7.6$ Hz, Ar−H), 7.43 (d, 2H, $J = 8.4$ Hz, Ar−H), 11.46 (br s, 1H). ^{13}CNMR ($CDCl_3$): δ 14.3, 21.0, 21.4, 22.8, 24.8, 29.1, 29.4, 29.5, 32.0, 34.1, 37.9, 120.2, 129.1, 129.6, 130.5, 133.6, 135.4, 135.8, 139.2, 152.4 (NHC=O), 177.9 (C=O). IR (KBr): 3167 (w), 2922 (m), 1721 (s), 589 (m) cm^{-1}. $C_{25}H_{34}N_2O_2$ (394.56): calcd. C 76.10%, H 8.69%, N 7.10%; found: C 76.12%, H 8.54%, N 7.17%.
6e	m.p. 104–106 °C; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, $J = 7.2$ Hz, CH_3), 1.22 (m, 12H, 6CH_2), 1.55 (m, 2H, CH_2), 2.12 (m, 2H, CH_2), 3.77 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 6.83 (m, 2H, Ar−H), 7.03 (m, 2H, Ar−H), 7.21 (m, 1H, Ar−H), 7.41 (m, 1H, Ar−H), 7.48 (m, 2H, Ar−H), 11.44 (br s, 1H, NH). ^{13}CNMR ($CDCl_3$): δ 14.3, 22.8, 24.6, 29.1, 29.4, 29.48, 29.52, 32.0, 36.8, 55.6, 55.9, 112.1, 114.2, 121.3, 121.7, 127.1, 130.7, 131.3, 151.9, 155.5, 156.2 (NH−C=O), 178.1 (C=O). IR (KBr): 3181 (w), 2923 (m), 1716 (s), 1661 (w), 1603 (m) cm^{-1}. $C_{25}H_{34}N_2O_4$ (426.56): calcd. C 70.40%, H 8.03%, N 6.57%; found: C 70.48%, H 7.95%, N 6.53%.
6f	m.p. 108–110 °C; H NMR ($CDCl_3$): δ 0.87 (t, 3H, $J = 7.2$ Hz, CH_3), 1.10–1.31 (m, 16H, 8CH_2), 1.59 (m, 2H, CH_2), 2.12 (m, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 6.90 (m, 2H, Ar−H), 7.03 (m, 3H, Ar−H), 7.21 (m, 1H, Ar−H), 7.42 (m, 1H, Ar−H), 8.26 (m, 1H, Ar−H), 11.82 (br s, 1H, NH). ^{13}CNMR ($CDCl_3$): δ 4.3, 22.8, 24.7, 29.14, 29.44, 29.47, 29.55, 29.74, 32.1, 36.9, 110.2, 112.1, 120.2, 121.1, 121.2, 123.5, 127.4, 128.1, 130.6, 130.7, 148.8, 151.7, 155.6 (NH−C=O), 177.7 (C=O). IR (KBr): 3175 (w), 2918 (m), 1716 (s), 1670 (w), 1601 (m) cm^{-1}. $C_{27}H_{38}N_2O_4$ (454.61): calcd. C 71.34%, H 8.43%, N 6.16%; found: C 71.33%, H 8.40%, N 6.19%.
1g	m.p. 128–130 °C; ^{1}H NMR ($CDCl_3$): δ 7.13, (t, 1H, $J = 7.6$ Hz, Ar−H), 7.16–7.22 (m, 4H, Ar−H), 7.23–7.29 (m, 6H, Ar−H), 7.35 (t, 2H, $J = 8.4$ Hz, Ar−H), 7.62 (d, 2H, $J = 7.6$ Hz, Ar−H), 11.41 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 120.5, 124.4, 128.0, 128.1, 128.4, 128.9, 129.2, 130.3, 130.6, 135.9, 137.8, 138.7, 152.2 (NH−C=O), 174.3 (C=O). IR (KBr): 2918 (w), 1704 (s), 1611 (w), 1576 (m) cm^{-1}. $C_{20}H_{16}N_2O_2$ (316.36): calcd. C 75.93%, H 5.10%, N, 8.85%; found: C 75.81%, H 5.11%, N, 8.80%.

(*Continued*)

Table 6. Continued.

Entry	Spectral data
1h	m.p. 135–137 °C; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.13 (t, 1H, $J = 7.2$ Hz, Ar−H), 7.25 (m, 4H, Ar−H), 7.34 (m, 3H, Ar−H), 7.63 (d, 2H, $J = 8.4$ Hz, Ar−H), 7.75 (d, 2H, $J = 7.6$ Hz, Ar−H), 7.99 (m, 2H, Ar−H). ^{13}CNMR ($CDCl_3$): δ 21.7, 120.5, 124.6, 126.9, 127.3, 129.2, 129.4, 129.6, 130.4, 132.3, 138.2, 142.5, 144.6, 166.1 (NH−C=O), 171.4 (C=O). IR (KBr): 2918 (w), 1650 (s), 1524 (m) cm^{-1}. $C_{21}H_{18}N_2O_2$ (330.39): calcd. C 76.34%, H 5.49%, N 8.48%; found: C 76.29%, H 5.53%, N 8.45%.
5h	m.p. 137–139 °C; ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.77 (d, 2H, $J = 8.8$ Hz, Ar−H), 6.87 (d, 2H, $J = 9.2$ Hz, Ar−H), 6.99 (d, 2H, $J = 8.0$ Hz, Ar−H), 7.08 (d, 2H,$J = 8.8$ Hz, Ar−H), 7.18 (d, 2H, $J = 8.0$ Hz, Ar−H), 7.51 (d, 2H, $J = 9.2$ Hz, Ar−H), 11.28 (brs, 1H, NH). ^{13}CNMR ($CDCl_3$): δ 21.6, 55.6, 114.2, 114.3, 122.1, 128.4, 128.7, 131.0, 131.2, 131.7, 133.2, 140.9, 152.7, 156.5, 159.2 (NH−C=O), 174.4 (C=O). IR (KBr): 3176 (w), 1714 (s), 1648 (m), 1513 (m) cm^{-1}. $C_{23}H_{22}N_2O_4$ (390.44): calcd. C 70.75%, H 5.68%, N 7.17%; found: C 70.71%, H 5.72%, N 7.22%.

acetate (15 ml). The ethyl acetate layer was washed with water (3×5 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product **1d**. Pure product was obtained after passing through a short column of silica gel using a mixture of hexane:ethylacetate (92:8) to furnish the pure product in 62% yield.

4.3. *Characterization of compounds*

1a, **1c**, **2a**, **3a**, **5a**, **8a**, **17a**, **19a**, **20a**, **21a** (*15*) and **7a** (*14*) are reported. For those compounds, ^{1}H NMR, ^{13}C NMR, IR (KBr) and m.p. data have been correlated with the reported one. Regioisomeric mixtures were analysed by measuring the integration of N-acyl as well as NH peaks. The spectral data (^{1}H NMR, ^{13}C NMR, IR (KBr) and HRMS) of the remaining compounds are given in Table 6.

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