

Efficient *S*-Acylation of Thiourea

David J. Jones^{a,b,e}Uday B. Rao Khandavilli^{a,b}Eileen M. O'Leary^cSimon E. Lawrence^{a,b,e}Timothy P. O'Sullivan^{*a,b,d}

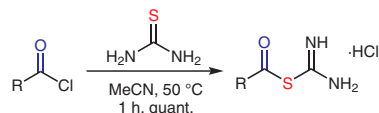
^a School of Chemistry, University College Cork, Cork, Ireland
tim.osullivan@ucc.ie

^b Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland

^c Department of Physical Sciences, Cork Institute of Technology, Cork, Ireland

^d School of Pharmacy, University College Cork, Cork, Ireland

^e Synthesis and Solid-State Pharmaceutical Centre, University College Cork, Cork, Ireland



Key Features:

- Rapid, quantitative reaction which avoids chromatographic purification
- 21 structurally diverse examples were synthesised
- Novel analogues of common NSAIDs were prepared by this method

Received: 16.08.2018

Accepted after revision: 12.09.2018

Published online: 17.10.2018

DOI: 10.1055/s-0037-1610370; Art ID: so-2018-d0048-l

License terms:

Abstract Efficient *S*-acylation of thiourea using a variety of acid chlorides is reported. Structurally diverse aryl and alkyl substrates are compatible with this methodology. Confirmation that acylation occurs exclusively on the sulfur atom of thiourea is provided by single-crystal X-ray crystallographic analysis.

Key words isothioureas, thiourea, organosulfur, sulfur transfer

The thiourea motif is ubiquitous in organic chemistry. In particular, *S*-alkyl- and *S*-aryl isothioureas are widely employed as precursors to sulfur-containing heterocycles¹ such as thiazoles² and thiouracils.³ They are also useful in the preparation of sulfonyl chlorides,⁴ thiols,⁵ sulfides,⁶ disulfides⁷ and guanidines.⁸ The sulfur transfer reagent 3-mercaptopropionitrile is typically accessed from the corresponding isothioureas derivative.⁹ More recently, *S*- and *N*-substituted thioureas have been incorporated into various organocatalysts to facilitate asymmetric induction through hydrogen bonding.¹⁰ Interestingly, isobenzofuran-substituted isothioureas undergo unusual base-mediated thermal rearrangement reactions to form isoindoles¹¹ while isothioureas substituted indolones rearrange under similar conditions to form thiazoles.¹² The corresponding benzofuran-2-one analogues likewise rearrange to furnish 1,3-isothiazolidin-4-ones.¹³

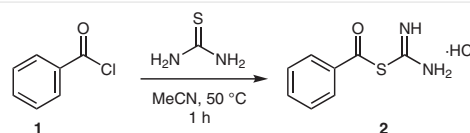
S-Alkyl and *S*-aryl thioureas are notable molecules in their own right. They are known to inhibit a number of enzyme systems including nitric oxide synthase (NOS)¹⁴, monoamine oxidase (MAO)¹⁵ and H3 histamine receptors.¹⁶ Their inhibitory effect on multidrug resistant bacterial strains has also been described.¹⁷ Isothioureas have been found to disrupt biofilm formation in *P. aeruginosa*.¹⁸ Indol-

amine 2,3-dioxygenase (IDO), an enzyme that is overexpressed in several disease states including cancer, is inhibited by a range of simple *S*-alkyl isothioureas.¹⁹ Allylic isothioureas have displayed potent antileukemia activity.²⁰

While the formation of *S*-alkyl isothioureas is well-studied,^{1a,1c,5f,20,21} there remains few systematic studies on the synthesis of *S*-acyl derivatives. It has previously been shown that thiourea reacts quantitatively with acetyl or benzoyl chloride to form the corresponding acylated thiourea adducts.²² However, it was not clear whether substitution had occurred on the sulfur or nitrogen atoms and these compounds were not characterised by modern techniques.

Herein, we report an efficient method for the selective *S*-acylation of thiourea, and we confirm that acylation occurs exclusively on the sulfur atom. Our method can be applied to a broad range of substrates, including the non-steroidal anti-inflammatory drugs (NSAIDs) Indomethacin, Aspirin, Diclofenac and Ibuprofen.

In the course of our studies on sulfur transfer reagents, we observed the formation of *S*-benzoyl isothioureas hydrochloride (**2**) on addition of benzoyl chloride (**1**) to a warm solution of thiourea in acetonitrile (Scheme 1).



Scheme 1 Synthesis of *S*-benzoyl isothioureas hydrochloride (**2**)

The reaction proceeded rapidly with instantaneous precipitation of the product, which was isolated in quantitative yield without need for further purification. It was subsequently found that treatment of thiourea with a range of aryl-substituted acid chlorides furnished the corresponding

S-acyl isothiureas **2–9** quantitatively (Scheme 2). The reaction tolerates aromatic acid chlorides with either electron-donating or electron-withdrawing substituents. This route also provides access to more sterically hindered *ortho*-substituted products, such as **4**. Evidence that acylation had occurred exclusively on the sulfur atom, rather than on either of the nitrogen atoms, was provided by the apparent equivalence of the chemical shift values for the isothiuronium protons in the ^1H NMR spectrum of **2–9**. No evidence for the formation of the *N*-acylated regioisomers was present in the spectra of the crude reaction mixtures. Additionally, recrystallisation of **5** and subsequent single-crystal X-ray diffraction confirmed that acylation had indeed occurred at the sulfur atom (see the Supporting Information for details) (Figure 1). The equivalent C–N bond lengths in S-acyl isothiurea **5** confirm the delocalization of the cation across the amidine portion of the molecule (Figure 2). These bond lengths are similar to those of previously described alkyl isothiurea **10**.²³ The S–C–N bond angle is smaller in **5** than in **10**, perhaps reflecting the influence of the adjacent carbonyl group. The hydrogen bond network in **5** is constructed through bridging chloride ions *via* N–H⋯Cl hydrogen bonding. Although the quaternary carbon signal of the isothiuronium group was not always apparent by ^{13}C NMR analysis, extending the relaxation delay from 1.00 second to 4.00 seconds allowed for the detection of the isothiuronium carbon in **2** (see the Supporting Information).

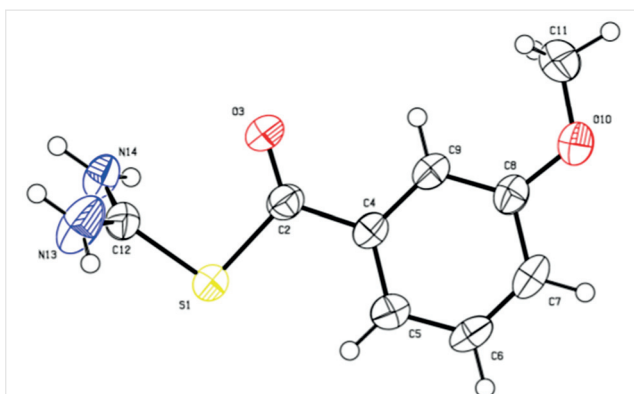


Figure 1 Crystal structure of **5**, demonstrating that acylation has occurred at the sulfur atom

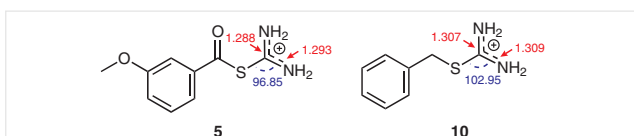
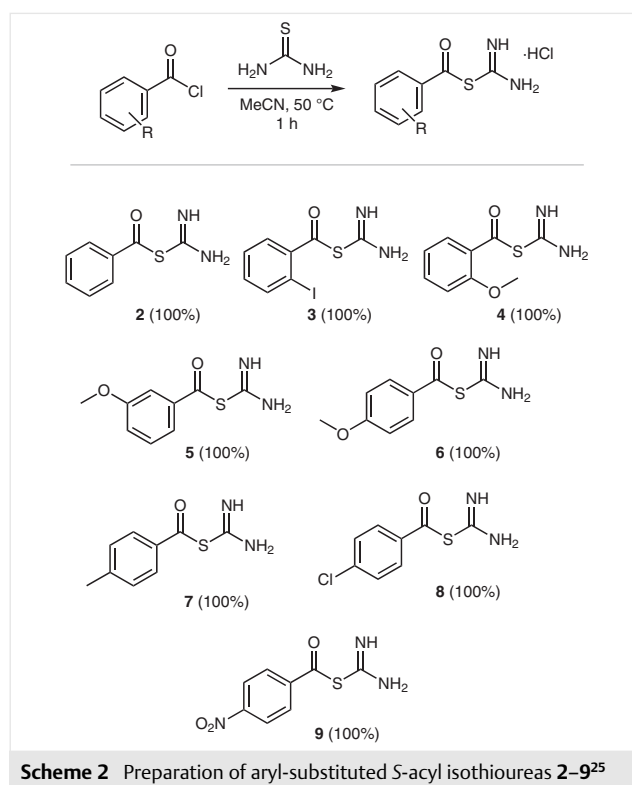


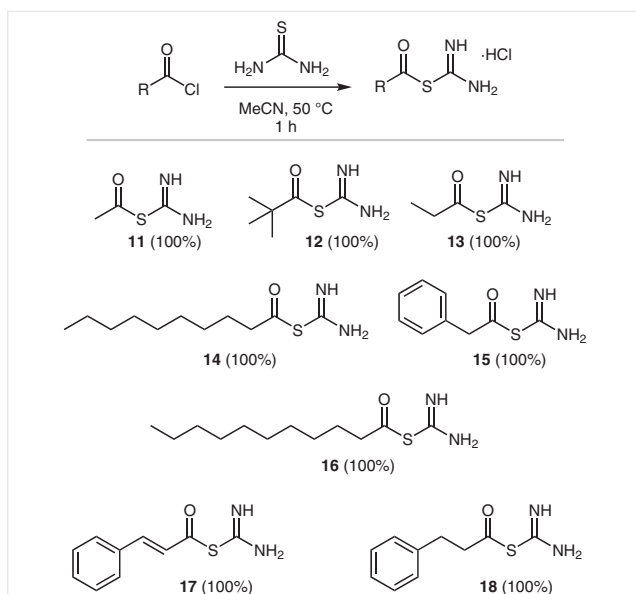
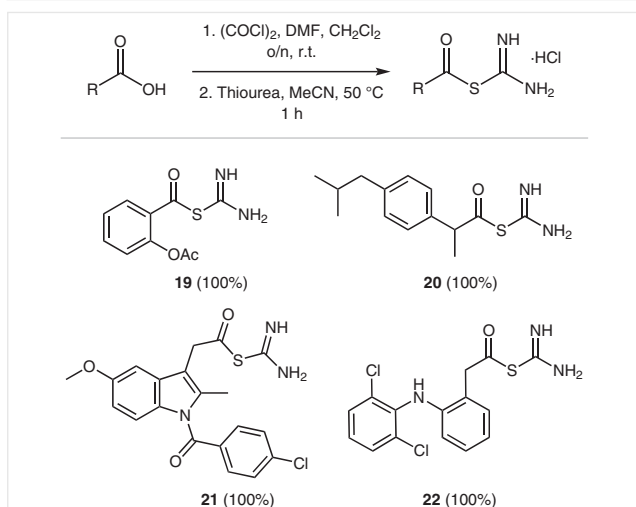
Figure 2 Comparison of bond lengths (in red) and S–C–N bond angles (in blue) between **5** and **10**²³

Alkyl- and alkyl-aryl-substituted acid chlorides were subjected to the same conditions, affording **11–18** in quantitative yields (Scheme 3). As part of an ongoing effort in our laboratory to develop novel anti-inflammatory agents, we wondered whether this methodology could also be applied to some common NSAIDs. Diclofenac, Aspirin, Ibuprofen and Indomethacin were converted into their corresponding acid chlorides with oxalyl chloride in the presence of a catalytic amount of *N,N*-dimethylformamide.²⁴ Addition of the resultant acid chlorides to a solution of thiourea in acetonitrile furnished NSAID derivatives **19–22**, again in quantitative yields, with no apparent difference in reactivity (Scheme 4).



Scheme 2 Preparation of aryl-substituted S-acyl isothiureas **2–9**²⁵

In conclusion, a method for the facile synthesis of S-acyl isothiureas has been described. The reactions proceed quantitatively, and the resulting solids are isolated without the need for further purification. We have shown that acylation occurs exclusively on the sulfur atom through crystallographic analysis. Several common NSAIDs were converted into their S-acyl isothiurea derivatives using this approach.

Scheme 3 Preparation of alkyl and aryl-alkyl derivatives 11–18²⁵Scheme 4 Preparation of NSAID derivatives 19–22²⁵

Funding Information

This research received financial support from Science Foundation Ireland under Grant Numbers 12/RC/2275, 05/PICA/B802/EC07, 14/US/E2915 (UBRK) and the UCC Strategic Research Fund (UBRK and DJJ).

Acknowledgment

Dr Lorraine Bateman and Dr Denis Lynch are acknowledged for assistance with NMR spectroscopy.

Supporting Information

Details of the crystallographic analysis of compound **5** and full characterisation for all novel compounds with associated ¹H and ¹³C NMR spectra can be found in the Supporting Information. The crystallographic data associated with this article have been deposited with the Cambridge Crystallographic Data Centre, CCDC 1586073. Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610370>.

References and Notes

- (a) Krishnamurthy, M.; Basavaprabhu, ; Sharanabai, K. M.; Sureshbabu, V. V. *Tetrahedron Lett.* **2014**, *55*, 5609. (b) Kim, H.-Y.; Kwak, S. H.; Lee, G.-H.; Gong, Y.-D. *Tetrahedron* **2014**, *70*, 8737. (c) Alcolea, V.; Garnica, P.; Palop, J.; Sanmartín, C.; González-Peñas, E.; Durán, A.; Lizarraga, E. *Molecules* **2017**, *22*, 1314. (d) Friebe, M.; Mahmood, A.; Spies, H.; Berger, R.; Johannsen, B.; Mohammed, A.; Eisenhut, M.; Bolzati, C.; Davison, A.; Jones, A. G. *J. Med. Chem.* **2000**, *43*, 2745. (e) Wu, Y.-J.; Guernon, J.; Park, H.; Thompson, L. A. *J. Org. Chem.* **2016**, *81*, 3386.
- (a) Hickey, S. M.; White, J. M.; Pfeffer, F. M.; Ashton, T. D. *Synlett* **2015**, *26*, 1759. (b) Takaya, J.; Mio, K.; Shiraiishi, T.; Kurokawa, T.; Otsuka, S.; Mori, Y.; Uesugi, M. *J. Am. Chem. Soc.* **2015**, *137*, 15859. (c) Xu, Z.; Guo, J.; Yang, Y.; Zhang, M.; Ba, M.; Li, Z.; Cao, Y.; He, R.; Yu, M.; Zhou, H.; Li, X.; Huang, X.; Guo, Y.; Guo, C. *Eur. J. Med. Chem.* **2016**, *123*, 309.
- (a) Palanki, M. S. S.; Erdman, P. E.; Manning, A. M.; Ow, A.; Ransone, L. J.; Spooner, C.; Suto, C.; Suto, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1645. (b) Zanatta, N.; Fortes, A. S.; Bencke, C. E.; Marangoni, M. A.; Camargo, A. F.; Fantinel, C. A.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2015**, *47*, 827. (c) Kaur, H.; Balzarini, J.; de Kock, C.; Smith, P. J.; Chibale, K.; Singh, K. *Eur. J. Med. Chem.* **2015**, *101*, 52. (d) Murai, K.; Miyazaki, S.; Fujioka, H. *Tetrahedron Lett.* **2012**, *53*, 3746.
- (a) Liu, C.; Guo, W.; Shi, X.; Kaium, M. A.; Gu, X.; Zhu, Y. Z. *Eur. J. Med. Chem.* **2011**, *46*, 3996. (b) Qiu, K.; Wang, R. *Synthesis* **2015**, *47*, 3186. (c) Yang, Z.; Zheng, Y.; Xu, J. *Synlett* **2013**, *24*, 2165.
- (a) Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2429. (b) Murphy Kessabi, F.; Beaudegnies, R.; Quaranta, L.; Lamberth, C. *Tetrahedron Lett.* **2016**, *57*, 5511. (c) Floyd, N.; Vijayakrishnan, B.; Koeppe, J. R.; Davis, B. G. *Angew. Chem. Int. Ed.* **2009**, *48*, 7798. (d) Brown, T. J.; Chapman, R. F.; Cook, D. C.; Hart, T. W.; McLay, I. M.; Jordan, R.; Mason, J. S.; Palfreyman, M. N.; Walsh, R. J. A. *J. Med. Chem.* **1992**, *35*, 3613. (e) Minard, T. A.; Oswin, C. T.; Waldie, F. D. C.; Howell, J. K.; Scott, B. M. T.; Mondo, D. D.; Sullivan, R. J.; Stein, B.; Jennings, M.; Schlaf, M. *J. Mol. Catal. A: Chem.* **2016**, *422*, 175. (f) Zong, J.; Mague, J. T.; Pascal, Jr. R. A. *Tetrahedron* **2017**, *73*, 455. (g) Rotili, D.; De Luca, A.; Tarantino, D.; Pezzola, S.; Forgione, M.; Morozzo della Rocca, B.; Falconi, M.; Mai, A.; Caccuri, A. M. *Eur. J. Med. Chem.* **2015**, *89*, 156.
- (a) Su, X.; Pradaux-Caggiano, F.; Vicker, N.; Thomas, M. P.; Halem, H.; Culler, M. D.; Potter, B. V. L. *ChemMedChem* **2011**, *6*, 1616. (b) Marciniec, K.; Pawełczak, B.; Latocha, M.; Skrzypek, L.; Maciążek-Jurczyk, M.; Boryczka, S. *Molecules* **2017**, *22*, 300. (c) Lee, Y. S.; Kim, H. Y.; Kim, Y.; Seo, J. H.; Roh, E. J.; Han, H.; Shin, K. J. *Bioorg. Med. Chem.* **2012**, *20*, 4921.

- (7) (a) Emerson, D. W.; Bennett, B. L.; Steinberg, S. M. *Synth. Commun.* **2005**, *35*, 631. (b) Chukicheva, I. Y.; Sukrusheva, O. V.; Shumova, O. A.; Mazaletskaia, L. I.; Shevchenko, O. G.; Kuchin, A. V. *Russ. J. Gen. Chem.* **2016**, *86*, 2052. (c) Younai, A.; Fettingner, J. C.; Shaw, J. T. *Tetrahedron* **2012**, *68*, 4320.
- (8) Aoyagi, N.; Furusho, Y.; Endo, T. *Synlett* **2014**, 25, 983.
- (9) (a) Jones, D. J.; O'Leary, E. M.; O'Sullivan, T. P. *Tetrahedron Lett.* **2017**, *58*, 4212. (b) Raz, R.; Rademann, J. *Org. Lett.* **2011**, *13*, 1606.
- (10) (a) Najda-Mocarska, E.; Zakaszewska, A.; Janikowska, K.; Makowiec, S. *Synth. Commun.* **2018**, *48*, 14. (b) Supady, A.; Hecht, S.; Baldauf, C. *Org. Lett.* **2017**, *19*, 4199. (c) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051. (d) Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, 1185. (e) Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, 5919.
- (11) Váňa, J.; Sedlák, M.; Padělková, Z.; Hanusek, J. *Tetrahedron* **2012**, *68*, 9808.
- (12) Kammel, R.; Tarabová, D.; Brož, B.; Hladíková, V.; Hanusek, J. *Tetrahedron* **2017**, *73*, 1861.
- (13) Kammel, R.; Hanusek, J. *Heterocycles* **2014**, *89*, 1183.
- (14) (a) Southan, G. J.; Szabo, C. *Biochem. Pharmacol.* **1996**, *51*, 383. (b) Southan, G. J.; Zingarelli, B.; O'Connor, M.; Salzman, A. L.; Szabo, C. *Br. J. Pharmacol.* **1996**, *117*, 619. (c) Southan, G. J.; Szabo, C.; Thiernemann, C. *Br. J. Pharmacol.* **1995**, *114*, 510. (d) Jang, D.; Szabo, C.; Murrell, G. A. *Eur. J. Pharmacol.* **1996**, *312*, 341.
- (15) (a) Mostert, S.; Mentz, W.; Petzer, A.; Bergh, J. J.; Petzer, J. P. *Bioorg. Med. Chem.* **2012**, *20*, 7040. (b) Booysen, H. P.; Moraal, C.; Terre'Blanche, G.; Petzer, A.; Bergh, J. J.; Petzer, J. P. *Bioorg. Med. Chem.* **2011**, *19*, 7507.
- (16) Ganellin, C. R.; Hosseini, S. K.; Khalaf, Y. S.; Tertiuik, W.; Arrang, J. M.; Garbarg, M.; Ligneau, X.; Schwartz, J. C. *J. Med. Chem.* **1995**, *38*, 3342.
- (17) (a) Nicholson, A.; Perry, J. D.; James, A. L.; Stanforth, S. P.; Carnell, S.; Wilkinson, K.; Anjam Khan, C. M.; De Soyza, A.; Gould, F. K. *Int. J. Antimicrob. Agents* **2012**, *39*, 27. (b) Barker, C. A.; Allison, S. E.; Zlitni, S.; Nguyen, N. D.; Das, R.; Melacini, G.; Capretta, A. A.; Brown, E. D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2426.
- (18) (a) Bonez, P. C.; Rossi, G. G.; Bandeira, J. R.; Ramos, A. P.; Mizdal, C. R.; Agertt, V. A.; Dalla Nora, E. S. S.; de Souza, M. E.; dos Santos Alves, C. F.; dos Santos, F. S.; Gündel, A.; de Almeida Vaucher, R.; Santos, R. C. V.; de Campos, M. M. A. *Microb. Pathog.* **2017**, *111*, (Supplement C) 6. (b) Bonez, P. C.; Ramos, A. P.; Nascimento, K.; Copetti, P. M.; Souza, M. E.; Rossi, G. G.; Agertt, V. A.; Sagrillo, M. R.; Santos, R. C. V.; Campos, M. M. A. *Microb. Pathog.* **2016**, *99*, (Supplement C) 14.
- (19) Matsuno, K.; Takai, K.; Isaka, Y.; Unno, Y.; Sato, M.; Takikawa, O.; Asai, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5126.
- (20) Ferreira, M.; Assunção, L. S.; Silva, A. H.; Filippin-Monteiro, F. B.; Creczynski-Pasa, T. B.; Sâ, M. M. *Eur. J. Med. Chem.* **2017**, *129*, (Supplement C) 151.
- (21) (a) Jamaledini, A.; Mohammadizadeh, M. R. *Tetrahedron Lett.* **2017**, *58*, 78–81. (b) Ingham, R. J.; Riva, E.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2012**, *14*, 3920. (c) Huang, Y.; Zhang, J.; Yu, Z.; Zhang, H.; Wang, Y.; Lingel, A.; Qi, W.; Gu, J.; Zhao, K.; Shultz, M. D.; Wang, L.; Fu, X.; Sun, Y.; Zhang, Q.; Jiang, X.; Zhang, J.; Zhang, C.; Li, L.; Zeng, J.; Feng, L.; Zhang, C.; Liu, Y.; Zhang, M.; Zhang, L.; Zhao, M.; Gao, Z.; Liu, X.; Fang, D.; Guo, H.; Mi, Y.; Gabriel, T.; Dillon, M. P.; Atadja, P.; Oyang, C. *J. Med. Chem.* **2017**, *60*, 2215. (d) Geies, A. A.; Abdel, Moneam, M. I.; Kamal, El-Dean, A. M.; Zaki, R. M.; Abd, El-Naem, E. E. *J. Heterocycl. Chem.* **2017**, *54*, 2012. (e) Mousdis, G. A.; Ganotopoulos, N.-M.; Barkaoui, H.; Abid, Y.; Psycharis, V.; Savvidou, A.; Raptopoulou, C. P. *Eur. J. Inorg. Chem.* **2017**, 3401. (f) Elacqua, E.; Manning, K. B.; Lye, D. S.; Pomarico, S. K.; Morgia, F.; Weck, M. *J. Am. Chem. Soc.* **2017**, *139*, 12240. (g) Abul-Futouh, H.; Almazahreh, L. R.; Harb, M. K.; Görls, H.; El-khateeb, M.; Weigand, W. *Inorg. Chem.* **2017**, *56*, 10437. (h) Manos-Turvey, A.; Al-Ashtal, H. A.; Needham, P. G.; Hartline, C. B.; Prichard, M. N.; Wipf, P.; Brodsky, J. L. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5087. (i) Tong, S.; Zhang, M.; Wang, S.; Yin, R.; Yu, R.; Wan, S.; Jiang, T.; Zhang, L. *Eur. J. Med. Chem.* **2016**, *123*, (Supplement C) 849.
- (22) (a) Dixon, A. E.; Hawthorne, J. J. *Chem. Soc., Trans.* **1907**, *91*, 122. (b) Dixon, A. E.; Taylor, J. J. *Chem. Soc., Trans.* **1920**, *117*, 720.
- (23) Hemalatha, P.; Veeravazhuthi, V. *Acta Crystallogr., Sect. E: Struct. Rep. Online*; **2008**, *64*, 1805. CCDC Deposition Number: 695520.
- (24) Biancalana, L.; Batchelor, L. K.; De Palo, A.; Zacchini, S.; Pampaloni, G.; Dyson, P. J.; Marchetti, F. *Dalton Trans.* **2017**, 12001.
- (25) General Procedure: To a stirred solution of thiourea (78 mg, 1.00 mmol, 1.00 equiv) in acetonitrile (10 mL) at 50 °C was added a solution of the required acid chloride (1.00 mmol, 1.00 equiv) in acetonitrile (10 mL) dropwise. The resulting thick suspension was allowed to stir at this temperature for a further one hour to ensure complete reaction. After one hour, the reaction mixture was cooled on ice and then vacuum filtered. The cake was washed with ethyl acetate (2 × 10 mL) to afford the products. The products were obtained quantitatively unless otherwise stated.

Representative Examples:

S-(3-Methoxybenzoyl)isothiuronium Chloride (5)

Mp 166–168 °C (MeCN).

¹H NMR (400 MHz, DMSO-*d*₆): δ = 3.80 (s, 3 H, OCH₃), 7.19 (dd, *J* = 8.15, 1.83 Hz, 1 H, ArC(2)*H*), 7.39–7.44 (m, 2 H, overlapping ArC(6)*H* and ArC(3)*H*), 7.53 (d, *J* = 8.15 Hz, 1 H, ArC(4)*H*), 9.62 (bs, 4 H, NH₂=C-NH₂). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 55.2, 113.8, 118.9, 121.5, 129.7, 132.1, 159.2, 167.1. IR (KBr): 3329, 3281, 3163, 3085, 2954, 2836, 1697, 1609, 1583, 1526, 1470, 1420, 1311, 1293, 1267, 1051, 755 cm⁻¹. HRMS (ESI⁺): *m/z* calcd. for C₉H₁₁N₂O₂S⁺: 211.0536; found: 211.0528. Anal. Calcd. for C₉H₁₁N₂O₂ClS: C, 44.00; H, 4.10; N, 11.40; Found: C, 44.31; H, 4.18; N, 11.71.

S-(Decanoyl)isothiuronium Chloride (14)

Mp 115–117 °C (MeCN).

¹H NMR (400 MHz, DMSO-*d*₆): δ = 0.86 (t, *J* = 7.51 Hz, 3 H, CH₃(10)), 1.24 (m, 12 H, CH₂(9–4)), 1.46–1.50 (m, 2 H, CH₂(3)), 2.18 (t, *J* = 7.88 Hz, 2 H, CH₂(2)), 9.18 (bs, 4 H, NH₂=C-NH₂). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 13.9, 22.1, 24.5, 28.5, 28.6, 28.7, 31.2, 33.6, 174.5. IR (KBr): 3385, 3261, 3175, 3031, 2822, 2859, 1748, 1676, 1427, 732 cm⁻¹. HRMS (ESI⁺): *m/z* calcd for C₁₁H₂₃N₂OS: 231.1531; Found: 231.1536. Anal. Calcd for C₁₁H₂₃N₂OClS: C, 49.52; H, 8.69; N, 10.50; Found: C, 49.18; H, 8.75; N, 10.71.

Indomethacin Analogue 21

Mp 168–171 °C (MeCN).

¹H NMR (400 MHz, DMSO-*d*₆): δ = 2.22 (s, 3 H, ArCH₃), 3.67 (s, 2 H, CH₂), 3.76 (s, 3 H, OCH₃), 6.72 (dd, *J* = 8.18, 1.33 Hz, 1 H, C(6)*H*), 6.92 (d, *J* = 8.18 Hz, 1 H, C(7)*H*), 7.05 (d, *J* = 1.33 Hz, 1 H, C(4)*H*), 7.64–7.70 (m, 4 H, Ar(2', 3', 5' and 6')*H*). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 13.2, 29.5, 55.4, 101.7, 111.3, 113.4, 114.6, 116.5, 129.0, 130.2, 130.71, 131.1, 134.1, 135.1, 137.6, 155.5,

167.8, 172.0. IR (KBr): 3332, 3312, 2952, 1727, 1687, 1657, 1482, 1308, 1227, 1047, 792 cm^{-1} . HRMS (ESI⁺): m/z calcd for $\text{C}_{20}\text{H}_{19}\text{ClN}_3\text{O}_3\text{S}^+$: 416.0830; Found: 416.0851. Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3\text{S}$: C, 53.10; H, 4.23; N, 9.29; Found: C, 53.33; H 4.29; N, 9.45