


 Cite this: *RSC Adv.*, 2025, 15, 44246

# Base-mediated three-component system for the synthesis of *S*-substituted *N*-acyl ureas

 Malibongwe P. Shandu,<sup>a</sup> Andile R. Ngwenya,<sup>a</sup> Jairus L. Lamola<sup>b</sup> and Paseka T. Moshapo<sup>b\*</sup>

 Received 13th October 2025  
 Accepted 6th November 2025

DOI: 10.1039/d5ra05563f

rsc.li/rsc-advances

*N*-Acyl ureas are crucial intermediates in the synthesis of biologically active molecules, and their preparation traditionally relies on multi-step synthesis under reflux conditions. Here, we report a three-component system that combines widespread alkyl halides, thiourea and carbamoyl chlorides. Crucial to this strategy is the synthesis of specific *S*-substituted *N*-acyl ureas *via* the formation of the isothiuronium salt intermediates. This developed three-component system affords scalable and functional group-tolerant reactivity, furnishing the desired products in good to excellent yields under mild conditions.

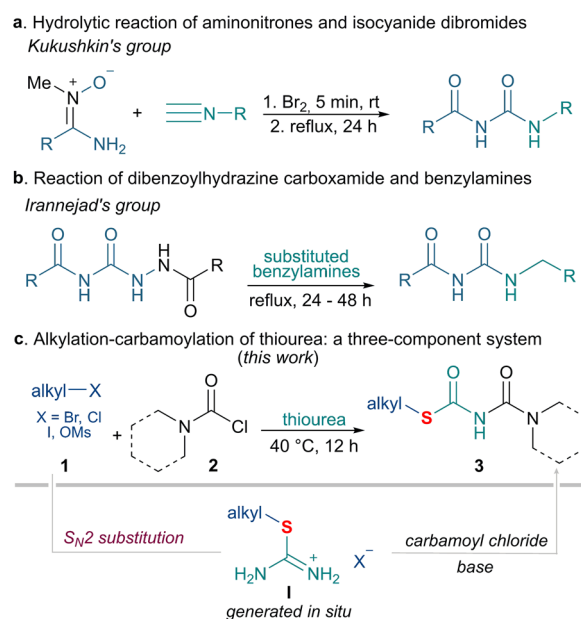
## Introduction

*N*-Acyl ureas are important intermediates in a wide range of biologically active molecules.<sup>1–5</sup> For example, the *N*-acyl urea motif is incorporated in molecules active as anti-cancer,<sup>6–8</sup> anti-inflammatory,<sup>9,10</sup> anti-convulsant<sup>11</sup> and anti-diabetic<sup>12,13</sup> agents. Therefore, the advancement of efficient synthetic methods for their preparation is of considerable interest. Over the years, a cascade of strategies for synthesising these motifs has been reported.<sup>14–23</sup> Traditional synthetic methods typically involve the acylation of amides and ureas,<sup>14–17</sup> nucleophilic substitution of acyl carbamates,<sup>18</sup> coupling of carboxylic acids with cyanamides and carbodiimides,<sup>19,20</sup> and the addition of amines to acyl isocyanates.<sup>21,22</sup> However, these approaches require transition-metal catalysts as well as multi-step synthesis.

To overcome these limitations, a few alternative methods have been developed.<sup>24–28</sup> Notably, Kukushkin's group developed a transition metal-free, one-pot stepwise *N*-acyl urea synthesis using a reactive aminonitrone-isocyanide system. However, substrate scope was limited and reflux conditions were required (Scheme 1a).<sup>29</sup> Recently, Irannejad's group reported the use of dibenzoylhydrazine carboxamide and benzylamines under reflux conditions, although this protocol is limited to five *N*-benzyl-*N*-acyl ureas (Scheme 1b).<sup>30</sup> Clearly, the establishment of more protocols that would provide unique and efficient access to different classes of *N*-acyl ureas under mild conditions would be highly advantageous.

Here, we present a one-pot three-component system for the alkylation and carbamoylation of thiourea for the synthesis of *S*-

substituted *N*-acyl ureas (Scheme 1c). This study draws inspiration from the well-documented  $S_N2$  interaction of alkyl halides and thiourea to generate isothiuronium salts **I**.<sup>31–36</sup> We posited that a nucleophilic attack of the salt **I** on the carbamoyl chloride would furnish the desired product under mild reaction conditions (40 °C) (Scheme 1c). The reports that demonstrated the acylation of ureas using acyl halides further supported the feasibility of our plan.<sup>2,37</sup>



**Scheme 1** (a) Two-step hydrolytic synthesis of *N*-acyl ureas.<sup>29</sup> (b) Reaction of dibenzoylhydrazine carboxamide and benzylamines.<sup>30</sup> (c) One-step, three-component strategy for the preparation of *S*-substituted *N*-acyl ureas.

<sup>a</sup>Research Centre for Synthesis and Catalysis, Department of Chemical Sciences, University of Johannesburg, Cnr Kingsway Avenue and University Road, PO Box 524, Auckland Park, 2006, Johannesburg, South Africa. E-mail: pasekam@uj.ac.za

<sup>b</sup>Research and Technology (R&T) Sasol (Pty) Ltd, 1 Klasie Havenga Road, Sasolburg, 1947, South Africa



## Results and discussion

We began our investigations with benzyl bromide **1a**, *N,N*-dimethyl carbamoyl chloride **2a**, thiourea (**A**) and sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) as a base in tetrahydrofuran (THF) solvent at 40 °C for 12 h (Table 1). The reaction proceeded almost quantitatively, furnishing the desired *S*-substituted *N*-acyl urea product **3a** in 92% yield (entry 1). Attempts to use other solvents such as acetonitrile (MeCN) and ethanol (EtOH) (entries 2 and 3) as well as  $\text{H}_2\text{O}$  and diethyl ether ( $\text{Et}_2\text{O}$ ) (entries 4 and 5) resulted in either diminished **3a** yields (69–71%) or no product formation, respectively. Moreover, testing other bases resulted in comparable yields but lower efficiencies (entries 6–9, 81–89%). Further optimisation revealed that reactions conducted for 6 hours (entry 10, 77%) and lowering the temperature to 25 °C (entry 11, 75%) result in good yields, although still in lower efficiencies. Notably, no product was formed in the absence of thiourea and the base (entries 12 and 13). Given the lower effectiveness of greener solvents (entries 3 and 4), THF was selected due to its optimal reactivity.

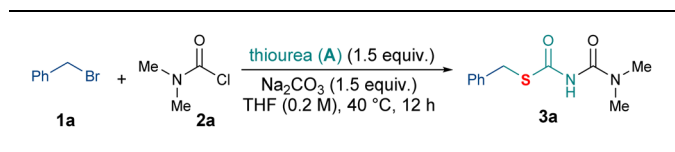
With the crystal structure of the desired product **3a** obtained from single-crystal X-ray analysis and optimised reaction conditions described in entry 1 of Table 1, we then explored the reaction scope for the *S*-substituted *N*-acyl urea synthesis using a diverse range of alkyl halides **1** with *N,N* dimethylcarbamoyl chloride **2a** (Fig. 1). The benzyl halides with different substituents on the phenyl ring; 4-nitro **1b**, 2-bromo **1c**, and 2,4,6-trimethyl **1d** moieties, reacted efficiently to form the corresponding **3b–3d** products with good to excellent yields (74–84%). The protocol also exhibited excellent tolerance towards cinnamyl bromide **1e** and valuable alkyl halides bearing a 5-

membered heterocyclic isoxazole ring **1f–1g**,<sup>38</sup> furnishing the corresponding products **3e** (83%), **3f** (88%) and **3g** (86%) in excellent yields. Furthermore, straight-chain alkyl halides such as iodomethane **1h**, 1-bromobutane **1i**, 1-bromopentane **1j** and 1-iodohexane **1k** efficiently reacted to give the corresponding products **3h–3k** in excellent yields (81–91%). However, longer chains such as 1-bromodecane, 1-bromoundecane and 1-bromohexadecane, as well as secondary alkyl halides, failed to produce the corresponding products **3**. This is presumably due to the inability of these long-chain and secondary alkyl halides to form the isothiuronium salt **I** under the identified reaction conditions (Table 1, entry 1). A complete list of failed substrates is reported in Fig. S1 of the SI. Additionally, straight-chain alkyl halides with reactive functional groups, including terminal alkenes **1l–1m**, alkyne **1n**, and cyano **1o** moieties, were suitable substrates, furnishing products **3l–3o** in good to excellent yields (77–93%), thus demonstrating the versatility of the developed protocol. Furthermore, the alkoxy group (**1p**) did not hinder the reaction (**3p**, 80%).

We next explored various carbamoyl chlorides **2** with benzyl bromide **1a** and thiourea (**A**), demonstrating the effectiveness of the developed reaction protocol (Fig. 1). For example, increasing the steric bulk around the carbamoyl *N*-centre did not impede the reaction, as demonstrated by the nearly quantitative product yields obtained in the coupling of carbamoyl chlorides containing *N,N*-diethyl **2q** and *N,N*-isopropyl **2r** moieties to produce products **3q** (85%) and **3r** (91%). Similarly, unsymmetrical carbamoyl chlorides **2s** and **2t** furnished products **3s** and **3t** in good to excellent yields (75–87%). Furthermore, with the abundance of *N*-cyclic motifs in biologically active molecules,<sup>39</sup> carbamoyl chlorides **2u–2w** with cyclic moieties were also well-tolerated, furnishing products **3u–3w** in excellent yields (82–89%). Finally, it was envisioned that this reaction protocol could be particularly suitable for gram-scale synthesis. Gratifyingly, a yield of 89% of product **3a** for a 20 mmol scale was obtained (Fig. 1). This yield is comparable to that observed for small-scale synthesis (1 mmol scale). Additionally, 2D NMR experiments, such as HMBC and HSQC, were conducted on product **3j**, and no structural rearrangements of the product were observed (see SI).

The effectiveness of this method was also demonstrated by developing a one-pot two-step telescoped procedure where benzyl bromide **1a** could be converted to product **3a** (93%). This telescoped procedure did not require any solvent evaporation but sequential addition of reagents (Fig. 2a). Furthermore, given the easy preparation and isolation of stable, odourless isothiuronium salts **I**,<sup>31</sup> product **3a** was obtained in excellent yield (85%) (see Section 4.5 of the SI). We then envisaged that the same isothiuronium salt **I** technique could provide reactivity to previously unreactive alkyl halides. Gratifyingly, the long straight-chained alkyl halides furnished the desired products in excellent yields (**3x**, 91% and **3y**, 93%) (Fig. 2b), demonstrating the easy access of the desired *S*-substituted *N*-acyl ureas **3x** and **3y** *via* isothiuronium salt **I** utility.

Finally, as a feature of our reaction design, it was anticipated that halides might be substituted by a different leaving group suitable for  $\text{S}_{\text{N}}2$  reactivity. In particular, alcohols **4** – abundant

Table 1 Optimisation and control experiments<sup>a</sup>

Entry	Variations	Yield <sup>b</sup> (%)
1	None	92
2	MeCN	71
3	EtOH	69
4	$\text{H}_2\text{O}$	0
5	$\text{Et}_2\text{O}$	0
6	$\text{Et}_3\text{N}$	81
7	DIPEA	84
8	DBU	86
9	$\text{K}_3\text{PO}_4$	89
10	6 h	77
11	25 °C	75
12	No thiourea	0
13	No base	0

<sup>a</sup> Optimisation and control experiments. Reactions performed on the scale: **1a** (1.5 mmol) and **2a** (1 mmol). <sup>b</sup> Reported yields are isolated yields. DIPEA: *N,N*-diisopropylethylamine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.



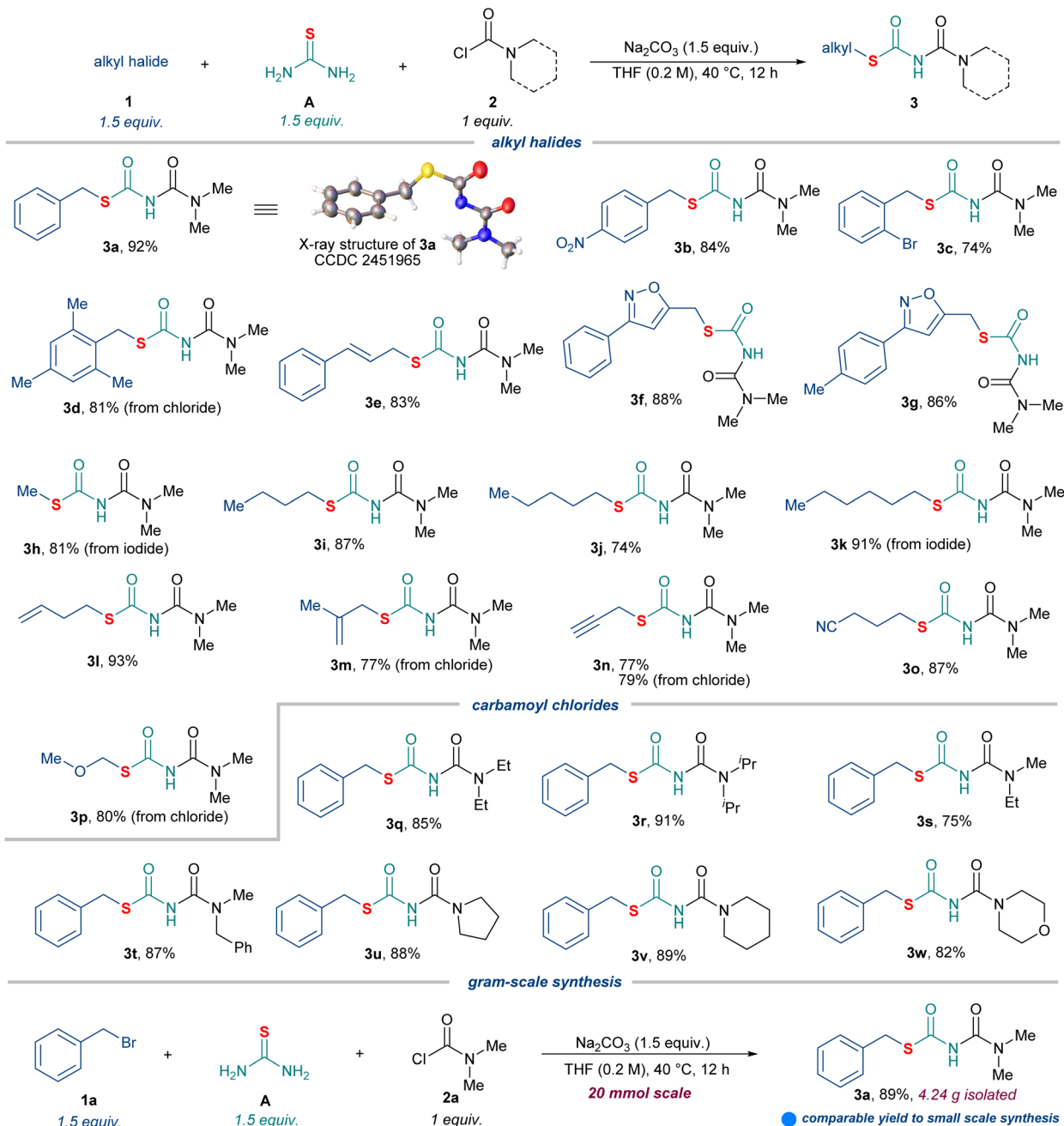


Fig. 1 S-Substituted *N*-acyl ureas synthesis substrate scope and gram-scale synthesis. Reactions performed on a 1 mmol scale. Alkyl bromides were used, unless otherwise stated. Reported yields are isolated yields.

feedstock with wide commercial availability – could serve as attractive precursors, a substitute for alkyl halides **1**.<sup>40</sup> To this end, we investigated alkyl mesylates **5** reactivity generated from one-step sulfonation of commercially available benzyl alcohol **4a**, 4-methoxybenzyl alcohol **4b**, and methanol **4c** (Fig. 2c). The reaction of benzyl mesylate **5a** with various carbamoyl chlorides furnished the desired products **3a** (74%), **3q** (79%), **3u** (65%), and **3w** (62%) in good to excellent yields. Lastly, 4-methoxybenzyl mesylate **5b** and methyl mesylate **5c** were also suitable electrophiles as demonstrated by the reaction with *N,N*-

dimethylcarbamoyl chloride **2a**, furnishing products **3h** (60%) and **3z** (70%), respectively, in good yields.

From the onset, it was envisioned that, mechanistically, the isothiuronium salt formation *via* S<sub>N</sub>2 reactivity of the alkyl halides **1** and thiourea (**A**) would be critical for this reaction (Fig. 2d).<sup>34,41</sup> We propose that the nucleophilic attack of the *in situ* generated isothiuronium salt **I** on the carbamoyl chloride **2** would follow.<sup>42</sup> The resulting iminium intermediate **II**, which, upon hydrolysis, would furnish the desired product **3**.



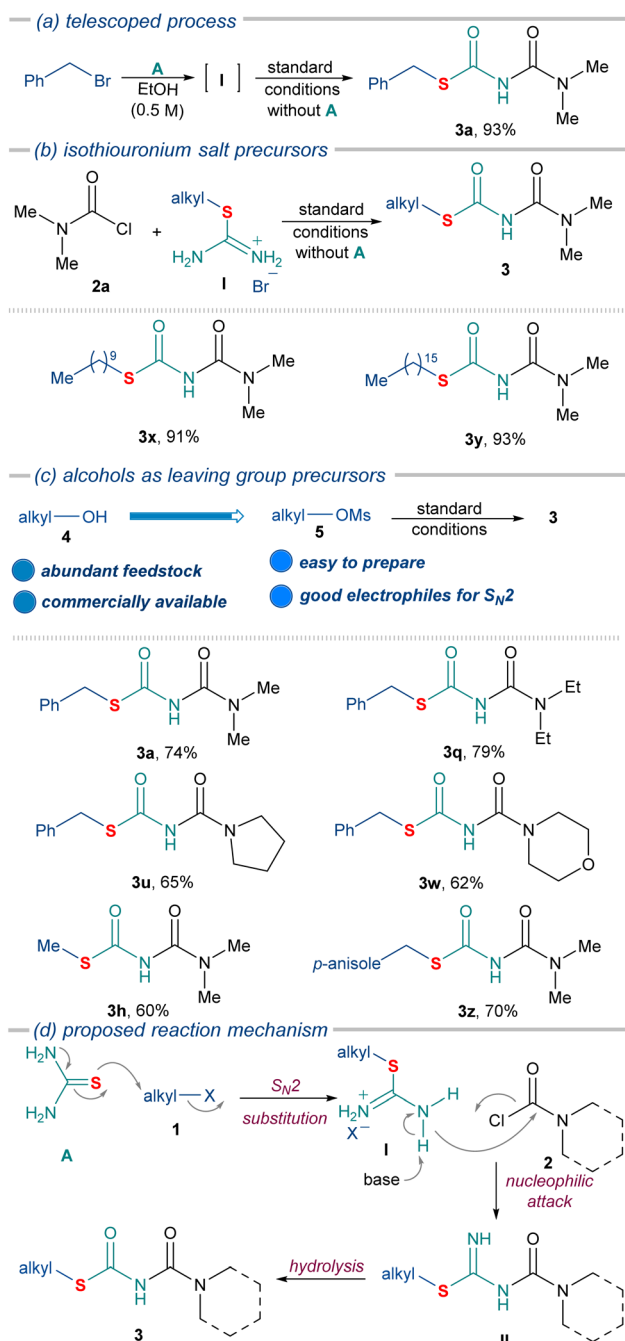


Fig. 2 (a) One-pot, two-step telescoped synthesis. (b) *S*-Alkyl isothiuronium salt utility. (c) Alkyl alcohols utility as leaving group precursors. (d) Proposed reaction mechanism. Reactions were performed on a 1 mmol scale. Reported yields are isolated yields.

## Conclusion

In summary, we report the one-pot, three-component synthesis of *S*-substituted *N*-acyl ureas using a combination of alkylation and carbamylation of the thiourea approach. Isolated product yields of up to 93% were obtained despite the electronic, steric, and structural variations of the alkyl halides and carbamoyl chloride substrates. Furthermore, we disclose the practicality of

this protocol by demonstrating the underutilised mesylates as precursors for the *in situ* formation of the isothiuronium salt **I**, delivering the desired *N*-acyl urea products in good to excellent yields. Given the importance of *N*-acyl ureas in bioactive structures, we anticipate that this protocol will find broad use in the synthetic community.

## Author contributions

Conceptualisation, M. P. S., J. L. L., and P. T. M.; methodology, M. P. S., and A. R. N. All authors have read and agreed to this version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

CCDC 2451965 (**3a**) contains the supplementary crystallographic data for this paper.<sup>43</sup>

The data supporting this article have been included in the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5ra05563f>.

## Acknowledgements

Research reported in this work was supported by the University of Johannesburg, Research Centre for Synthesis and Catalysis. We thank the National Research Fund (NRF) for financial support. We also thank Dr Banele Vatsha for X-ray single-crystal analysis, Mutshinyalo Nwamadi for NMR analysis, Dr Madelien Wooding for mass analysis (University of Pretoria), and Blessing Mkhonazi for the helpful discussions.

## Notes and references

- R. Feng, L. Huang, D. B. Qin, F. Zhou and Z. B. Dong, One-pot synthesis of *N*-acylated ureas using phenyliodine (III) diacetate (PIDA) as *N*-acylation agent, *Tetrahedron Lett.*, 2023, **127**, 154694–154700.
- H. G. Hacker, M. Meusel, M. Aschfalk and M. Gutschow, Solid-phase synthesis of disubstituted *N*-acylureas from resin-bound ureas and acyl chlorides, *ACS Comb. Sci.*, 2011, **13**, 59–64.
- E. M. Gayakwad, V. V. Patil, K. P. Patel and G. S. Shankarling, [Amberlyst-15 - (4Na<sub>2</sub>SO<sub>4</sub>-2H<sub>2</sub>O<sub>2</sub>-NaCl) Adduct]: Direct access to synthesize acylureas *via* oxidative amidation of aldehyde, *ChemistrySelect*, 2017, **2**, 9511–9515.
- U. D. Pete, C. M. Zade, J. D. Bhosale, S. G. Tupe, P. M. Chaudhary, A. G. Dikundwar and R. S. Bendre, Hybrid molecules of carvacrol and benzoyl urea/thiourea with potential applications in agriculture and medicine, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5550–5554.
- X. J. Mu, J. P. Zou, Q. F. Qian and W. Zhang, Regioselective synthesis of *N*-acetylureas by manganese(III) acetate



- reaction of 1,3-disubstituted thioureas, *Tetrahedron Lett.*, 2006, **47**, 2323–2325.
- 6 A. Solinas, H. Faure, H. Roudaut, E. Traiffort, A. Schoenfelder, A. Mann, F. Manetti, M. Taddei and M. Ruat, *J. Med. Chem.*, 2012, **55**, 1559–1571.
  - 7 D. Q. Song, Y. M. Wang, N. N. Du, W. Y. He, K. L. Chen, G. F. Wang, P. Yang, L. Z. Wu, X. B. Zhang and J. D. Jiang, Synthesis and activity evaluation of benzoylurea derivatives as potential antiproliferative agents, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 755–758.
  - 8 T. M. Caldwell, M. D. Kaufman, S. C. Wise, Y. Mi Ahn, M. M. Hood, W. P. Lu, W. Patt, T. Samarakoon, L. Vogeti, S. Vogeti, K. M. Yates, S. L. Bulfer, B. Le Bourdonnec, D. D. Smith and D. L. Flynn, Discovery of acyl ureas as highly selective small molecule CSF1R kinase inhibitors, *Bioorg. Med. Chem. Lett.*, 2022, **74**, 128929–128934.
  - 9 H. Gong, M. Yang, Z. Xiao, A. M. Doweiko, M. Cunningham, J. Wang, S. Habte, D. Holloway, C. Burke, D. Shuster, L. Gao, J. Carman, J. E. Somerville, S. G. Nadler, L. Salter-Cid, J. C. Barrish and D. S. Weinstein, Discovery of acylurea isosteres of 2-acylaminothiadiazole in the azaxanthene series of glucocorticoid receptor agonists, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3268–3273.
  - 10 A. Ranise, S. Schenone, O. Bruno, F. Bondavalli, W. Filippelli, G. Falcone and B. Rivaldi, *N*-Acyl-*N*-phenyl ureas of piperidine and substituted piperidines endowed with anti-inflammatory and anti-proliferative activities, *Il Farmaco*, 2001, **56**, 647–657.
  - 11 T. Librowski, M. Kubacka, M. Meusel, S. Scolari, C. E. Muller and M. Gutschow, Evaluation of anticonvulsant and analgesic effects of benzyl- and benzhydryl ureides, *Eur. J. Pharmacol.*, 2007, **559**, 138–149.
  - 12 W. McCoull, P. Barton, A. J. Brown, S. S. Bowker, J. Cameron, D. S. Clarke, R. D. Davies, A. G. Dossetter, A. Ertan, M. Fenwick, C. Green, J. L. Holmes, N. Martin, D. Masters, J. E. Moore, N. J. Newcombe, C. Newton, H. Pointon, G. R. Robb, C. Sheldon, S. Stokes and D. Morgan, Identification, optimization, and pharmacology of acylurea GHS-R1a inverse agonists, *J. Med. Chem.*, 2014, **57**, 6128–6140.
  - 13 T. Klabunde, K. U. Wendt, D. Kadereit, V. Brachvogel, H.-J. Burger, A. W. Herling, N. G. Oikonomakos, M. N. Kosmopoulou, D. Schmoll, E. Sarubbi, E. von Roedern, K. Schonafinger and E. Defossa, Acyl ureas as human liver glycogen phosphorylase inhibitors for the treatment of type 2 diabetes, *J. Med. Chem.*, 2005, **48**, 6178–6193.
  - 14 P. F. Wiley, *J. Am. Chem. Soc.*, 1949, **71**, 1310–1311.
  - 15 K. Bjerglund, A. T. Lindhardt and T. Skrydstrup, Palladium-catalyzed *N*-acylation of monosubstituted ureas using near-stoichiometric carbon monoxide, *J. Org. Chem.*, 2012, **77**, 3793–3799.
  - 16 D. Liptrot, L. Alcaraz and B. Roberts, New Synthesis of aryl and heteroaryl *N*-acylureas *via* microwave-assisted palladium-catalysed carbonylation, *Adv. Synth. Catal.*, 2010, **352**, 2183–2188.
  - 17 T. Fuchikami and I. Ojima, New and direct route to 5-trifluoromethyl-5,6-dihydrouracils by means of palladium complex catalyzed “ureidocarbonylation” of 2-bromo-3,3,3-trifluoropropene, *Tetrahedron Lett.*, 1982, **23**, 4099–4100.
  - 18 S. Stokes and N. G. Martin, A simple and efficient synthesis of *N*-benzoyl ureas, *Tetrahedron Lett.*, 2012, **53**, 4802–4804.
  - 19 Z. Xiao, M. G. Yang, A. J. Tebben, M. A. Galella and D. S. Weinstein, Novel two-step, one-pot synthesis of primary acylureas, *Tetrahedron Lett.*, 2010, **51**, 5843–5844.
  - 20 S. Abbasi, M. K. Miraki, I. Radfar, M. Karimi and A. Heydari, Efficient synthesis of *N*-acylureas using copper oxide supported on magnetic nanoparticles in deep eutectic solvent, *ChemistrySelect*, 2018, **3**, 77–80.
  - 21 Z. Li, S. Xu, B. Huang, C. Yuan, W. Chang, B. Fu, L. Jiao, P. Wang and Z. Zhang, Pd-catalyzed carbonylation of acyl azides, *J. Org. Chem.*, 2019, **84**, 9497–9508.
  - 22 R. Maity, S. Naskar and I. Das, Copper(II)-catalyzed reactions of alpha-keto thioesters with azides *via* C-C and C-S bond cleavages: synthesis of *N*-acylureas and amides, *J. Org. Chem.*, 2018, **83**, 2114–2124.
  - 23 Z. L. Yang, X. L. Xu, X. R. Chen, Z. F. Mao and Y. F. Zhou, Silver-catalyzed acyl nitrene transfer reactions involving dioxazolones: direct assembly of *N*-acylureas, *Eur. J. Org. Chem.*, 2020, **2021**, 648–652.
  - 24 H. Yamamoto, K. Ishihara and T. Maki, Arylboronic acid-catalyzed direct condensation of carboxylic acids with ureas, *Synlett*, 2004, 1355–1358.
  - 25 R. Thapa, R. Flores, K. H. Cheng, B. Mochona and D. Sikazwe, Design and synthesis of new acyl urea analogs as potential  $\sigma$ 1R ligands, *Molecules*, 2023, **28**, 2319–2331.
  - 26 A. S. Singh, A. K. Agrahari, S. K. Singh, M. S. Yadav and V. K. Tiwari, An Improved Synthesis of Urea Derivatives from *N*-Acylbenzotriazole *via* Curtius Rearrangement, *Synthesis*, 2019, **51**, 3443–3450.
  - 27 A. L. I. Ramazani, F. Z. Nasrabadi, A. Rezaei, M. Rouhani, H. Ahankar, P. A. Asiabi, S. W. Joo, K. ŠLepokura and T. Lis, Synthesis of *N*-acylurea derivatives from carboxylic acids and *N,N'*-dialkyl carbodiimides in water, *J. Chem. Sci.*, 2015, **127**, 2269–2282.
  - 28 C. B. Singh, H. Ghosh, S. Murru and B. K. Patel, Hypervalent iodine(III)-mediated regioselective *N*-acylation of 1,3-disubstituted thioureas, *J. Org. Chem.*, 2008, **73**, 2481–2496.
  - 29 M. V. Il'in, L. A. Lesnikova, D. S. Bolotin, A. S. Novikov, V. V. Suslonov and V. Y. A. Kukushkin, A one-pot route to *N*-acyl ureas: a formal four-component hydrolytic reaction involving aminonitrones and isocyanide dibromides, *New J. Chem.*, 2020, **44**, 1253–1262.
  - 30 M. Valipour, A. M. Chippindale, A. Kouzeli and H. A. Irannejad, A new and facile synthesis of *N*-benzyl-*N'*-acylureas *via* reaction of dibenzoylhydrazine carboxamide and benzylamines, *Synth. Commun.*, 2021, **51**, 3004–3012.
  - 31 I. Tiefenbrunner, B. R. Brutiu, T. Stopka and N. Maulide, Isothiuronium-mediated conversion of carboxylic acids to cyanomethyl thioesters, *J. Org. Chem.*, 2023, **88**, 3941–3944.
  - 32 J. Merad, J. Matyasovsky, T. Stopka, B. R. Brutiu, A. Pinto, M. Drescher and N. Maulide, Stable and easily available



- sulfide surrogates allow a stereoselective activation of alcohols, *Chem. Sci.*, 2021, **12**, 7770–7774.
- 33 S. Fujisaki, I. Fujiwara, Y. Norisue and S. Kajigaeshi, A facile one-pot synthesis of sulfides from alkyl halides and alcohols using tetramethylthiourea, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2429–2430.
- 34 G. Lu and C. Cai, An odorless, one-pot synthesis of thioesters from organic halides, thiourea and benzoyl chlorides in water, *Adv. Synth. Catal.*, 2013, **355**, 1271–1276.
- 35 G. Lu, F. Chen and C. Cai, Thiourea in the construction of C–S bonds as part of an undergraduate organic chemistry laboratory course, *J. Chem. Educ.*, 2016, **94**, 244–247.
- 36 A. Monfared, S. Ahmadi, Z. Rahmani, P. D. K. Nezhad and A. Hosseini, Odorless, convenient and one-pot synthesis of thioethers from organic halides and thiourea, *J. Sulfur Chem.*, 2018, **40**, 209–231.
- 37 M. G. Voronkov, N. N. Vlasova, O. Y. Grigor'eva, L. I. Belousova and A. V. Vlasov, Acyl iodides in organic synthesis. Reactions of acetyl iodide with urea, thiourea, and their *N,N*-disubstituted derivatives, *Russ. J. Org. Chem.*, 2009, **45**, 486–490.
- 38 J. Zhu, J. Mo, H. Z. Lin, Y. Chen and H. P. Sun, The recent progress of isoxazole in medicinal chemistry, *Bioorg. Med. Chem.*, 2018, **26**, 3065–3075.
- 39 N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, A Review on recent advances in nitrogen-containing molecules and their biological applications, *Molecules*, 2020, **25**, 1909–1951.
- 40 A. L. Pace, F. Xu, W. Liu, M. N. Lavagnino and D. W. C. MacMillan, Iron-catalyzed cross-electrophile coupling for the formation of all-carbon quaternary centers, *J. Am. Chem. Soc.*, 2024, **146**, 32925–32932.
- 41 H. Firouzabadi, N. Iranpoor and M. Abbasi, A facile generation of C–S bonds *via* one-pot, odourless and efficient thia-Michael addition reactions using alkyl, aryl or allyl halides, thiourea and electron-deficient alkenes in wet polyethylene glycol (PEG 200) under mild reaction conditions, *Tetrahedron*, 2009, **65**, 5293–5301.
- 42 D. Kesuma, G. S. Putra and T. A. Yuniarta, Synthesis and cytotoxic activity of *N*-(2,4-dichloro)benzoyl-*N*'-phenylthiourea against human breast cancer cell line, *Thai J. Pharm. Sci.*, 2022, **42**, 173–176.
- 43 CCDC 2451965: Experimental Crystal Structure Determination, 2025, DOI: [10.5517/ccdc.csd.cc2n9gn3](https://doi.org/10.5517/ccdc.csd.cc2n9gn3).

