Communication

Journal of the Brazilian Chemical Society

https://dx.doi.org/10.21577/0103-5053.20260083

J. Braz. Chem. Soc. **2026**, *37-Spe2*, e-20260083, 1-8

N-(4-Bromophenyl) Ureas: A Mild Regioselective Synthesis and Antifungal Activity against *Colletotrichum lindemuthianum*

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A green, efficient, scalable and regioselective bromination of *N*-phenyl ureas was developed using NaBr/trichloroisocyanuric acid in methanol at room temperature. The protocol was effective to a range of substituted *N*-phenyl ureas, giving the corresponding *N*-(4-bromophenyl) ureas in up to 98% isolated yield under mild conditions. Among the products obtained, *N*-(4-bromophenyl)morpholine-4-carboxamide proved to be a valuable fungicide candidate against *Colletotrichum lindemuthianum*, an important pathogen responsible for causing anthracnose on common bean (*Phaseolus vulgaris*). The *in vitro* antifungal activity determined by the minimum inhibitory concentration (MIC = 63 mg mL^{-1}) gave the same result of the commercial fungicide thiophanate-methyl.

Keywords: halogenation, trichloroisocyanuric acid, green chemistry, phytopathogen, *Colletotrichum*, fungicide

Introduction

Urea derivatives are ubiquitous structures with applications in diverse branches of chemistry as agrochemicals,[1] organocatalysts,[2] uses in supramolecular chemistry,[3] intermediates in organic synthesis,[4] etc. In medicinal chemistry, urea derivatives exhibit antimicrobial, antibacterial, anti-inflammatory, anticonvulsive, anticancer, anti- human immunodeficiency virus (HIV) and antidiabetic activities, to name a few.[5] Among the various halogenated ureas, substances containing the *N*-haloaryl scaffold are useful building blocks in the synthesis of more complex structures[6] and play an important role as anticancer agents. In addition, *N*-phenyl ureas are one of the most important and widely used classes of fungicides worldwide for over 50 years.[1] Nowadays, more than 80% of marketed agrochemicals used for global crop protection have at least one carbon-halogen bond.[7] Consequently, due to their promising activities, *N*-haloaryl ureas have become targets and potentially interesting substrates of study and use as agrochemicals.[8] Figure 1 shows diverse *N*-haloaryl ureas that exhibit some sort of biological or pharmacological activity.

Frequently, *N*-haloaryl ureas have been prepared from halogenated substrates by the reaction of haloaryl isocyanates with amines[9] or halogenated anilines with isocyanates,[10] KOCN,[11] carbamates[12] or amines promoted by carbonyldiimidazole,[13] among others. Interestingly, there are few methodologies for the direct halogenation of *N*-aryl ureas.[14] In the specific case of *N*-(bromoaryl) ureas, they can be prepared by the reaction of the corresponding *N*-aryl ureas with tribromoisocyanuric acid (TBCA),[15] *N*-bromosuccinimide (NBS) catalyzed by Pd^{II},[16] KBr/phenyliodine(III) diacetate[17] and a photocatalytic oxidative bromination mediated by sodium anthraquinone sulfonate (SAS)[18] (Scheme 1). Although useful and efficient, these methodologies suffer from long reaction times, requiring special photochemical equipment or the use of expensive or not commercially available reagents.

In light of growing environmental concerns, green and efficient methodologies have attracted great interest over the last years. In this regard, trichloroisocyanuric acid (TCCA, Figure 2), an inexpensive solid used for disinfection, has

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Editor handled this article: Pedro de Castro (Guest)
This publication is part of the special issue "Organic Synthesis - BMOS"

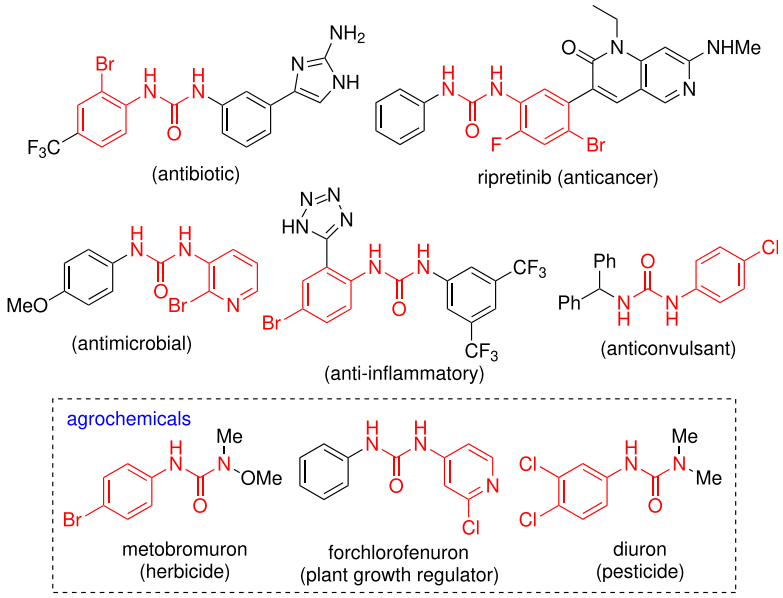
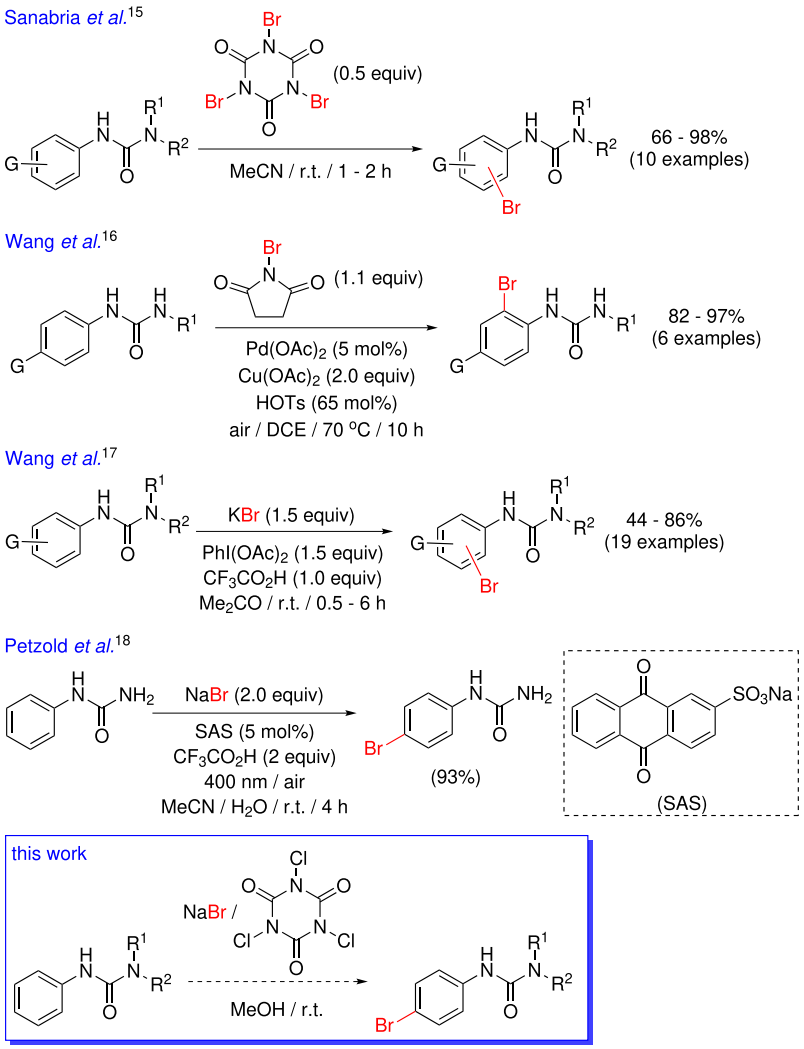


Figure 1. Selected examples of agrochemicals and pharmacologically active *N*-(haloaryl) ureas.



Scheme 1. Preparation of *N*-(bromoaryl) ureas.

been widely employed in diverse chlorinating reactions.[19] In addition to being safe and stable, TCCA is also readily available in pool supply and hardware stores and its use in organic reactions has some advantages, as it produces cyanuric acid at the end of the reactions, a harmless and biodegradable substance[20] that can be recycled to produce more TCCA through a green process.[21]

Some years ago, we showed that the NaCl/TCCA system is very efficient for a vicinal dichlorination of alkenes, without using molecular chlorine.[21] Furthermore, the association of TCCA with $NaNO_2$ or NH_4SCN is a mild alternative for electrophilic nitration[22] and thiocyanation[23] of arene rings, respectively. The role of TCCA in these reactions is to generate a powerful electrophilic species that can react even with weak nucleophiles, such as aromatic rings.

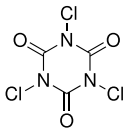


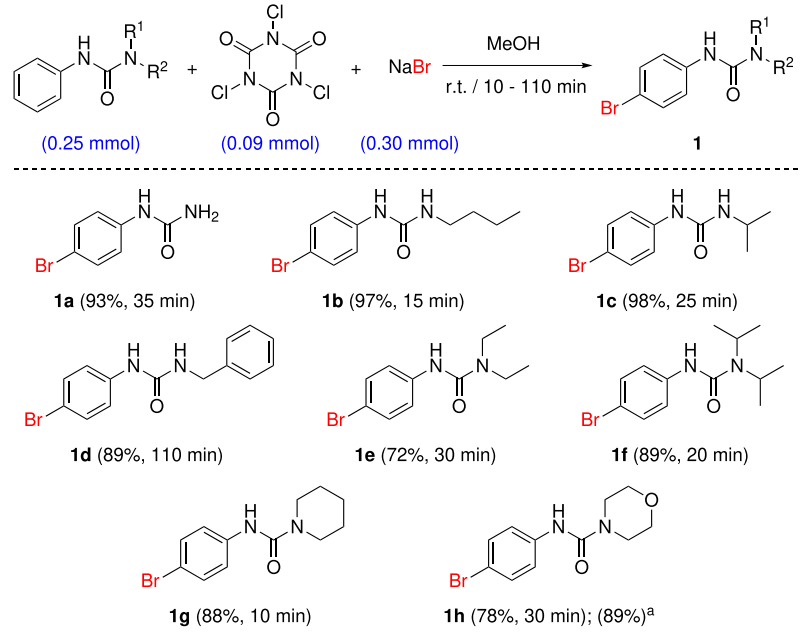
Figure 2. Trichloroisocyanuric acid (TCCA) structure.

The genus *Colletotrichum* comprises several phytopathogenic fungi that affect various plant species, especially in tropical or subtropical climates. Among these fungi is *Colletotrichum lindemuthianum*, which causes anthracnose to common bean (*Phaseolus vulgaris* L.), a crop of economic and social importance in Brazil.[24] Crop losses can reach 100% when seeds are infected by this fungus and sown in an environment favorable to fungal development.

Recently, we demonstrated that a halogenated 2-aminothiazole derivative is effective against *C. lindemuthianum*.[25] To further develop potentially bioactive compounds, we investigated the reaction of *N*-phenyl ureas with the NaBr/TCCA system to obtain brominated *N*-phenyl ureas, which were evaluated for their activity against the fungus *C. lindemuthianum*.

Results and Discussion

The results of the bromination reactions of *N*-phenyl ureas with different substitution patterns using the NaBr/TCCA system are summarized in Scheme 2. The reactions were carried out in 0.25 mmol scale at room temperature by stirring the *N*-phenyl urea, NaBr and trichloroisocyanuric acid in methanol, being the brominated products isolated after workup by a simple filtration of the reaction medium. To our delight, the products were obtained purely in up to 98% yield, needing no further purification, which demonstrates the simplicity and suitability of our protocol. All products are known compounds and were identified by their spectral data and melting points in comparison with previously reported. Rewardingly, although the ureido group is an *ortho/para* director in electrophilic aromatic substitution reactions (S_EAr), under our conditions, the regioselectivity was very high and only products with the bromine atom in the 4-position of the phenyl ring were



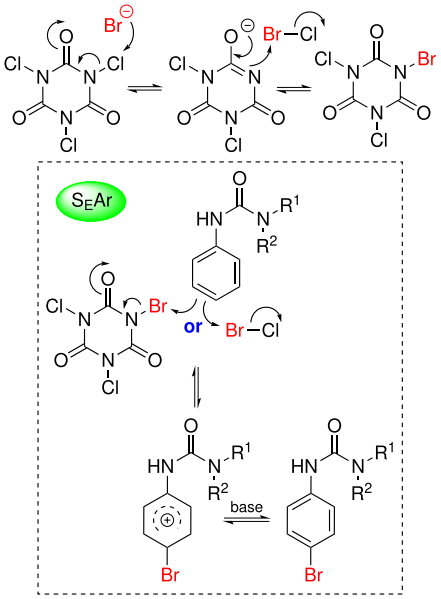
[a] Scaled up reaction using *N*-phenylmorpholine-4-carboxamide (1.03 g. 5.0 mmol), TCCA (0.42 g, 1.8 mmol) and NaBr (0.62 g, 6.0 mmol) in MeOH (100 mL) at r.t. for 90 min.

Scheme 2. Regioselective bromination of *N*-phenyl ureas with the NaBr/TCCA system.

obtained, without any regioisomeric *N*-(2-bromophenyl) ureas being detected by the analytical procedures employed (thin-layer chromatography (TLC), ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectra (HRMS)). To further demonstrate the efficiency of our methodology, we carried out a gram-scale synthesis of *N*-(4-bromophenyl)morpholine-4-carboxamide (**1h**, in Scheme 2), a valuable fungicide candidate against *C. lindemuthianum* (as demonstrated later). Therefore, the experimental procedure was scaled up to 5 mmol of *N*-(phenyl)morpholine-4-carboxamide as substrate to give **1h** in 89% (1.266 g), proving the scalability of the methodology.

The high *para*-regioselectivity obtained in our reactions is also observed when different electrophilic brominating reagents are employed with various arene substrates.[18,26] Similarly to our previous results on the selective iodination of *N*-phenyl ureas using the I_2/TCCA system,[14] no products resulting from the possible chlorination of *N*-phenyl ureas by TCCA[15] were observed in the crude reaction mixture. Furthermore, the halogenation reaction of *N*-benzyl-*N*'-phenylurea was highly chemoselective, affording only the brominated *N*-phenyl urea (**1d**), with no halogen incorporation detected in the benzyl ring. This result supports the low reactivity of benzylic rings in electrophilic halogenation reaction.[15]

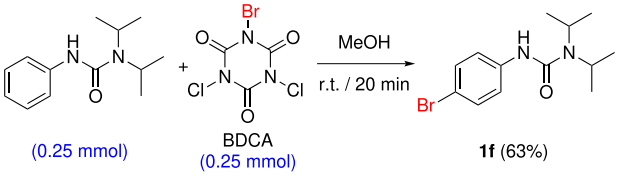
It is well known that *N*-phenyl ureas[15] and other aromatic rings[27] are readily chlorinated under mild conditions by trichloroisocyanuric acid. Therefore, since the NaBr/TCCA system has proven effective for the bromination of *N*-phenyl ureas, these results can only be rationalized by a prior reaction of NaBr with TCCA to produce a new powerful electrophilic brominating reagent that reacts with the aromatic ring. Although this reaction pathway is assumed to involve a traditional S_EAr, the nature of the brominating reagent is not clear (Scheme 3). A reasonable possibility is the fast formation of BrCl (from the direct reaction of NaBr with TCCA) as an active brominating regent.[21,28] Alternatively, the resulting cyanurate ion can further



Scheme 3. Possible pathway for the reaction of *N*-phenyl ureas with NaBr/TCCA.

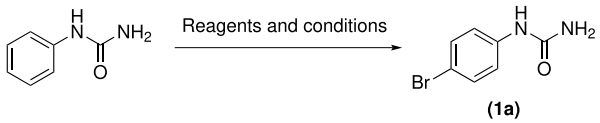
capture the more electrophilic bromenium ion from the interhalogen species to afford bromodichloroisocyanuric acid (BDCA)[29] *in situ*.[30] However, this last possibility seems unlikely, since control experiments reacting *N*-phenyl-*N*',*N*'-diisopropylurea with bromodichloroisocyanuric acid under the same conditions produced **1f** in considerably lower yield (63% *vs.* 89% using NaBr/TCCA) (Scheme 4).

Table 1 shows the usefulness of using the NaBr/TCCA system compared to previously reported protocols for the preparation of **1a** from *N*-phenylurea in the light of



Scheme 4. Reaction of *N*-phenyl-*N*',*N*'-diisopropylurea with bromodichloroisocyanuric acid.

Table 1. Comparison of different methodologies for bromination of *N*-phenylurea[a]



Reagents and conditions	Yield / %	AE / %	AEf / %	RME / %	Reference
Tribromoisocyanuric acid, MeCN, r.t.	84	83	70	57	15
NaBr, light, CF_3CO_2H, SAS, air, MeCN, H_2O, r.t.	93	61	57	35	18
NaBr, trichloroisocyanuric acid, MeOH, r.t.	93	68	63	56	this work

[a]Calculations can be found in the Supplementary Information section. AE: atom economy; AEf: atom efficiency; RME: reaction mass efficiency; r.t.: room temperature; SAS: sodium anthraquinone sulfonate.

the green chemistry metrics atom economy (AE),[31] atom efficiency (AEf),[32] and reaction mass efficiency (RME).[33] These metrics were selected because they indicate how efficiently a reaction was designed in relation to the reactants, taking into account the yields and the amounts employed, with higher values indicating a more environmentally friendly process.[34] As observed, our methodology presents the same yield as the photocatalytic reaction,[18] with some advantages, such as simpler workup, elimination of the need for any special photochemical equipment and a higher RME value. On the other hand, our methodology compared to that of Sanabria *et al*.,[15] which uses TBCA as a brominating reagent, also presents some advantages, such as readily available reagents and higher yield. Interestingly, although the use of NaBr/TCCA presents lower atom economy and atom efficiency, the RME values are the same. Therefore, considering the RME values, which is a more realistic metric to illustrate the greenness of the process,[33] our proposed methodology is noteworthy and consistent with the principles of green chemistry.[35]

The *in vitro* antifungal activity of the synthesized *N*-(4-bromoaryl) ureas against *C. lindemuthianum* was determined using the commercial fungicide thiophanate-methyl as a positive control and the results are shown in Table 2. It was observed that *N*-(4-bromophenyl) morpholine-4-carboxamide (**1h**) gave the best result, with minimum inhibitory concentration (MIC) similar to that observed for the positive control.

Table 2. Minimum inhibitory concentration (MIC) of synthesized *N*-(4-bromophenyl ureas (**1a**-**1h**), and the positive control (thiophanate-methyl)

N-(4-Bromophenyl) urea	MIC / (mg mL^{-1})
1a	500
1b	–[a]
1c	–[a]
1d	–[a]
1e	–[a]
1f	125
1g	–[a]
1h	62.5
Thiophanate-methyl	63

[a]Mycelial growth at all tested concentrations.

Conclusions

In conclusion, we have developed an efficient and simple methodology for a regioselective bromination of a variety of *N*-phenyl ureas. As advantages of our protocol, we could highlight the high *para* selectivity of the reaction, the use of safe, inexpensive and readily available reagents, mild and neutral reaction conditions, clean chemical transformation and easy workup (simple filtration of the pure product at the end of the reaction). The developed halogenation process is greener compared to previously methodologies, affording the desired pure products in good to excellent yields, without the need for any purification. One of the synthesized compounds (*N*-(4-bromophenyl)morpholine-4-carboxamide; **1h**) was as active against the fungus *C. lindemuthianum* as the commercial fungicide thiophanate-methyl, suggesting that it is potentially useful for the development of new fungicides.

Experimental

Materials and reagents

Commercially available reagents and solvents were used without further purification. Substituted *N*-phenyl ureas were prepared by reaction of phenyl isocyanate with the corresponding amines in CH_2Cl_2 or hexane.[14] The reactions were monitored by thin-layer chromatography (TLC) using precoated plates (silica gel 60 F-254, Salicycle), EtOAc/hexane 1:1 as eluent and were visualized under UV light.

Instrumentation

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance-500 (11.7 T) spectrometer at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR), using dimethyl sulfoxide (DMSO-d_6) or $CDCl_3$ as solvents and tetramethylsilane (TMS (Me_4Si)) as internal standard. The chemical shifts are expressed in ppm and the coupling constants (*J*) in Hz. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific QExactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer using positive electrospray ionization. Melting points (mp) were determined on a Fisatom 431 laboratory device and were not corrected.

Experimental conditions

General procedure for the preparation of *N*-(4-bromophenyl) ureas (**1**)

To a well stirred solution of the *N*-phenyl urea (0.25 mmol) and NaBr (31 mg, 0.30 mmol) in methanol (10 mL), TCCA (21 mg, 0.09 mmol) was slowly added at room temperature. After the end of the reaction

(determined by TLC), the pure product was precipitated by addition of 15% $NaHSO_3$ (10 mL) and isolated by simple filtration. The solid was washed with water and then dried. The purity of the products (> 95%) was confirmed by ^1H and ^{13}C NMR spectroscopy and HRMS.

N-(4-Bromofenil)urea (**1a**)[36]

White solid; yield 50 mg (93%); mp 270 °C (lit. mp 265-268 °C); Rf 0.06 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.55-7.21 (m, 4H), 6.01 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.0, 140.1, 131.2, 119.6, 112.2; HRMS (ESI) *m/z*, calcd. for $[C_7H_7BrN_2O + Na]^+$: 236.9634, found: 236.9643.

N-(4-Bromophenyl)-*N'*-butylurea (**1b**)[37]

White solid; yield 65 mg (97%); mp 184-185 °C (lit. mp 187-187.5 °C); Rf 0.54 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, DMSO-d_6) δ 8.92 (s, 1H), 7.36 (s, 4H), 6.46 (t, *J* 5.4 Hz, 1H), 3.05 (dd, *J* 12.5, 6.4 Hz, 2H), 1.43-1.21 (m, 4H), 0.87 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.2, 140.2, 131.2, 119.4, 111.9, 38.5, 31.8, 19.5, 13.6; HRMS (ESI) *m/z*, calcd. for $[C_{11}H_{15}BrN_2O + H]^+$: 271.0441, found: 271.0430.

N-(4-Bromophenyl)-*N'*-isopropylurea (**1c**)[38]

White solid; yield 63 mg (98%); mp 194-195 °C (lit. mp 198-200 °C); Rf 0.56 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.36 (m, 4H), 6.04 (d, *J* 8.0 Hz, 1H), 3.75 (m, 1H), 1.05 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.2, 140.2, 131.5, 129.8, 112.0, 41.5, 23.6; HRMS (ESI) *m/z*, calcd. for $[C_{10}H_{13}BrN_2O + H]^+$: 257.0290, found: 257.0285.

N-(4-Bromophenyl)-*N'*-benzylurea (**1d**)[39]

White solid; yield: 68 mg (89%); mp 199-201 °C (lit. mp 196-197 °C); Rf 0.47 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.37 (s, 4H), 7.34-7.22 (m, 5H), 6.67 (t, *J* 5.9 Hz, 1H), 4.30 (d, *J* 5.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.0, 140.2, 139.9, 131.3, 128.3, 127.1, 126.7, 119.6, 112.4, 42.7; HRMS (ESI) *m/z*, calcd. for $[C_{14}H_{13}BrN_2O + Na]^+$: 327.0103, found: 327.0089.

N-(4-Bromophenyl)-*N',N'*-diethylurea (**1e**)[40]

White solid; yield 49 mg (72%); mp 119-120 °C (lit. mp 123-124 °C); Rf 0.43 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* 8.9 Hz, 2H), 7.27 (d, *J* 8.9 Hz, 2H), 6.32 (s, 1H), 3.35 (q, *J* 7.2 Hz, 4H), 1.21 (t, *J* 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 138.6, 131.8, 121.5, 115.3, 41.8, 14.0; HRMS (ESI) *m/z*, calcd. for $[C_{11}H_{15}BrN_2O + H]^+$: 271.0441, found: 271.0440.

N-(4-Bromophenyl)-*N',N'*-diisopropylurea (**1f**)[41]

Yellow solid; yield 66 mg (89%); mp 155-157 °C (lit. mp 160-162 °C); Rf 0.62 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* 8.8 Hz, 2H), 7.27 (d, *J* 8.8 Hz, 2H), 6.18 (s, 1H), 3.96 (hept, *J* 6.8 Hz, 2H), 1.32 (d, *J* 6.9 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 138.6, 131.8, 121.3, 115.1, 45.7, 21.7; HRMS (ESI) *m/z*, calcd. for $[C_{13}H_{19}BrN_2O + H]^+$: 299.0753, found: 299.0740.

N-(4-Bromophenyl)piperidine-1-carboxamide (**1g**)[42]

Yellowish solid; yield: 62 mg (88%); mp 172-173 °C (lit. mp 176-178 °C); Rf 0.26 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* 7.0 Hz, 2H), 7.17 (d, *J* 7.0 Hz, 2H), 6.80 (s, 1H), 3.56 (s, 2H), 3.35 (s, 2H), 1.62 (m, 2H), 1.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 150.8, 128.6, 127.1, 122.3, 50.4, 43.2, 24.7; HRMS (ESI) *m/z*, calcd. for $[C_{12}H_{15}BrN_2O + H]^+$: 283.0446, found: 283.0443.

N-(4-Bromophenyl)morpholine-4-carboxamide (**1h**)[40]

White solid; yield 56 mg (78%); mp 195-197 °C (lit. mp 200-201); Rf 0.16 (EtOAc/hexane, 1:1); ^1H NMR (500 MHz, DMSO-d_6) δ 8.64 (s, 1H), 7.47-7.42 (m, 2H), 7.41-7.37 (m, 2H), 3.62-3.56 (m, 4H), 3.43-3.39 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.9, 139.9, 131.3, 121.4, 113.3, 66.0, 44.1; HRMS (ESI) *m/z*, calcd. for $[C_{11}H_{13}BrN_2O_2 + H]^+$: 285.0234, found: 285.0234.

Antifungal assay

Adapting the method described in the literature,[43] each compound was dissolved in dimethylsulfoxide (DMSO) to obtain a 2000 μg mL^{-1} stock solution, which was then diluted with M3S medium to 1000, 500, 250, 125, and 62.5 μg mL^{-1}. Commercial fungicide Cercobin 700WP™ (Ihara, Cajuru do Sul, Sorocaba (SP), Brazil; active ingredient: thiophanate-methyl) was dissolved in DMSO and diluted with M3S to 1400 μg mL^{-1}, which was diluted to 700, 350, 175, 87, and 44 μg mL^{-1}. The diluted concentrations of Cercobin 700WP™ correspond to 490, 245, 122.5, 60.9, and 30.8 μg mL^{-1} thiophanate-methyl, respectively. The negative control was a DMSO solution in M3S medium (5 μL + 95 μL, respectively). In a 96-well plate, each of the prepared solutions (100 μL) was added to an aqueous suspension (100 μL) containing *C. lindemuthianum* (1.2×10^6 conidia mL^{-1}) and kept in the dark at 23 °C for five days. For each compound, the minimum inhibitory concentration (MIC; the lowest concentration of each compound that inhibited fungal development) was determined by visual inspection without magnification, in duplicate.

Supplementary Information

Supplementary information (calculation of green chemistry metrics and NMR spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Data Availability Statement

The data supporting the findings of this study are available within the article and its SI section.

Acknowledgments

The authors thank CAPES, CNPq, FAPERJ and FAPEMIG for financial support and fellowships.

Author Contributions

Conceptualization: M. C. S. M.; funding acquisition: M. C. S. M. and D. F. O.; investigation: H. C. S., F. A. C. P. and E. A. S.; project administration: M. C. S. M. and D. F. O.; supervision: M. C. S. M. and D. F. O.; writing - original draft: M. C. S. M. and D. F. O.; writing - review and editing: H. C. S., M. C. S. M., D. F. O., F. A. C. P. and E. A. S.

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Submitted: March 31, 2026
Final version online: May 19, 2026