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A new and facile synthesis of N-Benzyl-N'-acylureas via Reaction of Dibenzoylhydrazine carboxamide and Benzylamines

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Abstract

Herein, we report a new method of synthesis of N-acylureas (**E1-5**) via reaction of dibenzoylhydrazine carboxamide (N,2-*bis*(4-methoxybenzoyl)hydrazine-1-carboxamide) (**C**) and various benzylamines. Preparation of dibenzoylhydrazine carboxamide was performed by the treatment of 5,6-diaryl-3-methylthio-1,2,4-triazine (**B**) with Oxone which leads to oxidation and triazine ring cleavage in high yield (82%). Five benzylamine derivatives containing different electron donating and withdrawing substituents were used in this study. Yields for the conversion of dibenzoylhydrazine carboxamide (**C**) to N-acylureas (**E1-5**) were in the range of 40-55%. The structures of the intermediates and final products were characterized and confirmed by NMR, mass spectrometry and single-crystal X-ray crystallography.

Keywords: N-Benzyl-N'-acylurea, Ureide, Carbamoylbenzamide, X-ray crystallography

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Introduction

N-Benzyl-N'-acylureas are a class of N-acylureas in which both amide nitrogen atoms have been substituted. N-acylureas are attractive substructures or scaffolds in drug discovery. Due to their resemblance in structure to peptidic bonds and their high hydrogen bonding potential,[1] they have a wide range of biological activities, such as antidiabetic effects by inhibiting human liver glycogen phosphorylase,[2] anticonvulsant,[3] anticancer and Hedgehog inhibiting[1] and histone deacetylase inhibitor[4] effects (Figure 1). Various synthetic routes reported in literature for the preparation of the N-acylurea derivatives are represented in Scheme 1. As shown in Scheme 1a, N-Acylureas can routinely be prepared either by reaction of N-acylisocyanates with amines or by reaction of isocyanates with amides under harsh conditions.[5] A recent method has reported the preparation of N-acylureas using dicyclohexylcarbodiimide (DCC) and various carboxylic acids using a copper-oxide nanocatalyst, but the urea -substituted alkyl side chains were only limited to the cyclohexyl group (Scheme 1b).[6] Interestingly, acyl carbamates are useful intermediates and can react with amines to produce N-acylureas (Scheme 1c). Here the acyl carbamates are prepared from diphenyl carbonate and sodium hydride. Both the preparation of diphenyl carbonate and its reactions with benzamides in the presence of sodium hydride need a critically dry condition.[7] An extensive study has also reported the synthesis of N-acylureas by solid-phase techniques using resin-bound urea derivatives and acylchlorides in which complicated, expensive and very reactive reagents have been utilized (Scheme 1d).[8] N-acylureas were also synthesized recently in a one-pot, four-component reaction with very reactive aminonitrones and isocyanide dibromides (Scheme 1e).[9]

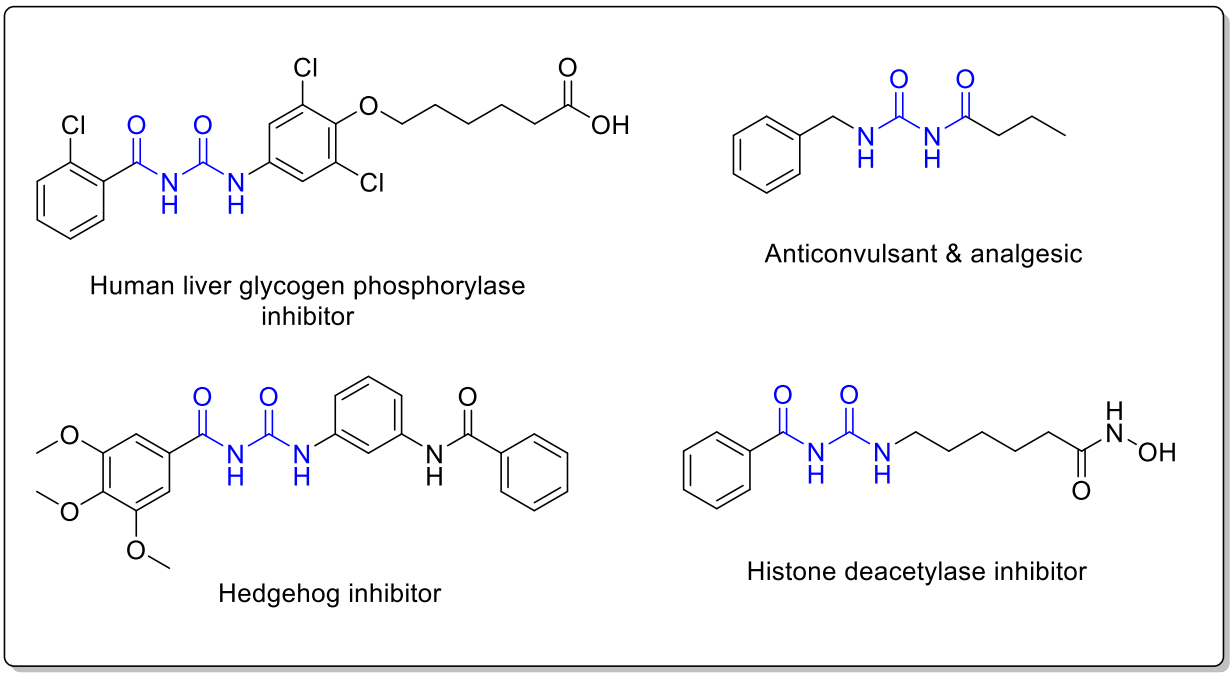
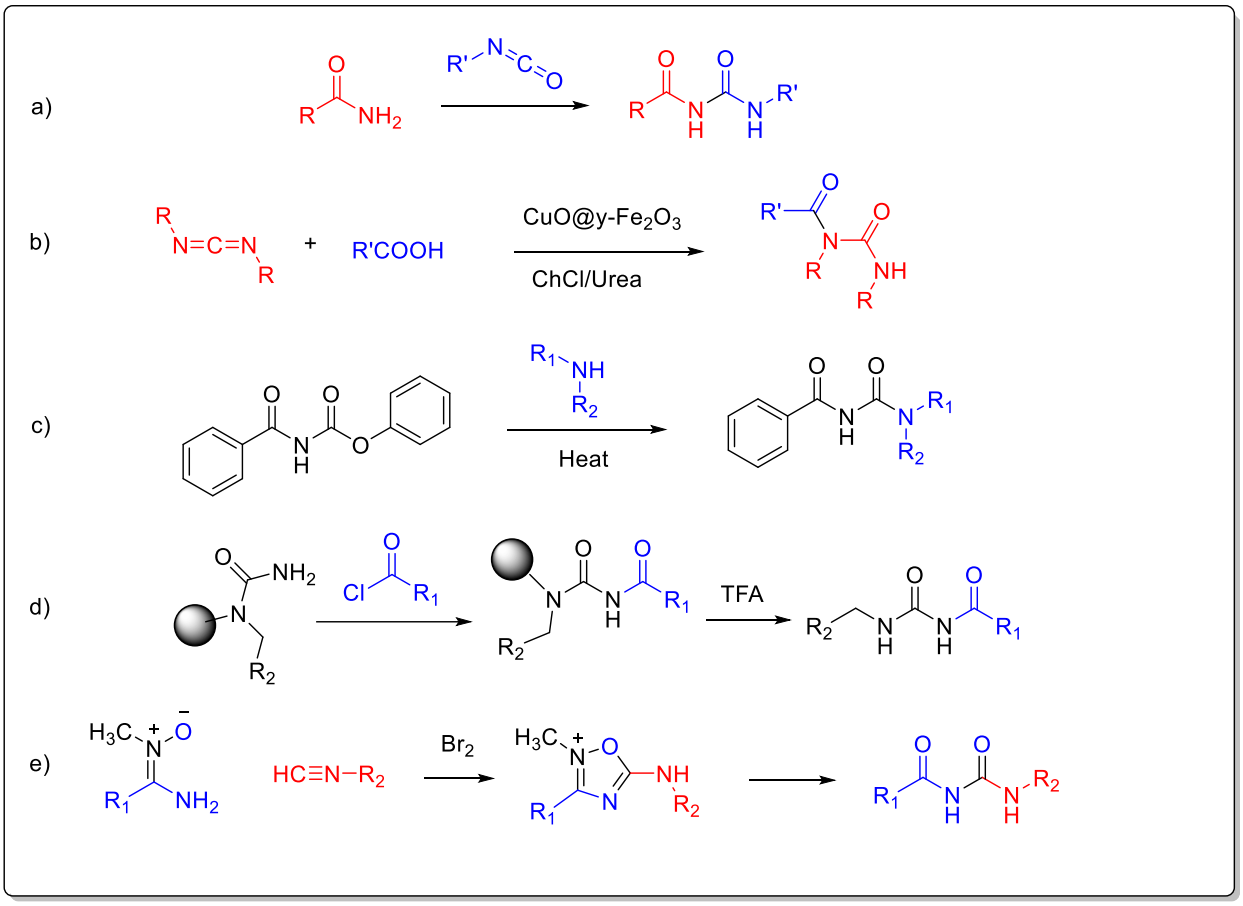
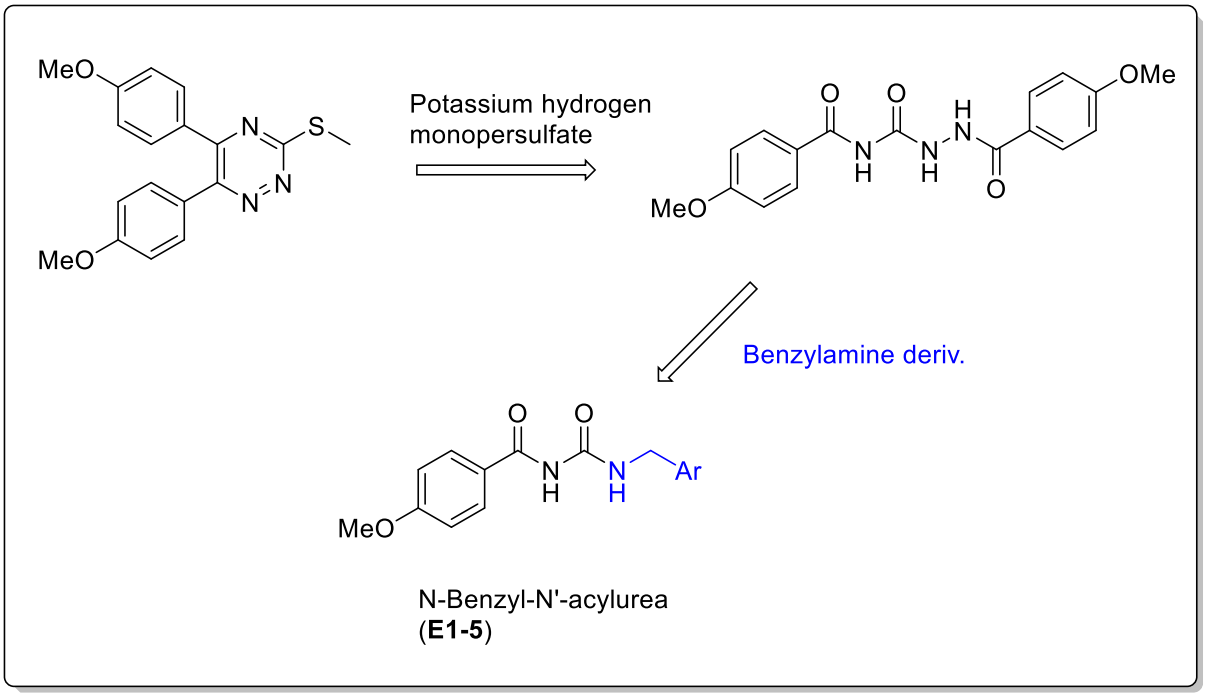


Figure 1. Some of the N-acylurea derivatives reported to have pharmacological activities.

Herein, we report a new and facile four-step preparation of a series of N-acylureas (N-benzyl)carbamoylbenzamides (**E1-5**)), starting from 1,2-bis(4-methoxyphenyl)ketone and adding benzylamine derivatives at the final stage (Scheme 2).



Scheme 1. Previous synthetic routes for the preparation of N-acylurea derivatives. For reactions a) to e), see references [5] – [9], respectively.

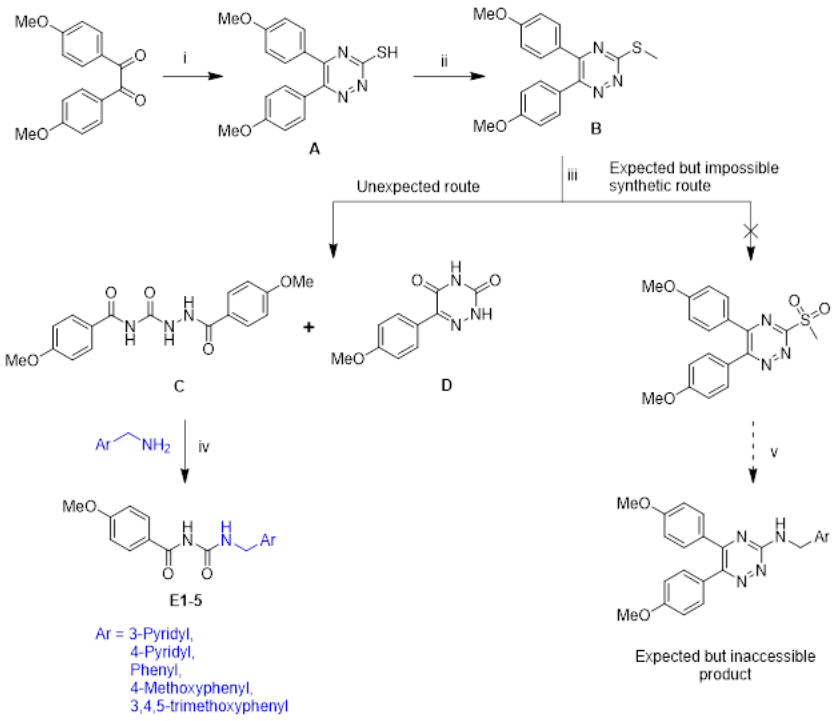


Scheme 2. Representation of the synthetic route for the preparation of the N-benzyl-N'-acylurea derivatives (**E1-5**) described in this study.

Results & Discussion

In our ongoing program to prepare benzylamines substituted at position 3 of the 5,6-diaryl-1,2,4-triazine derivatives, 3-methylthio-5,6-diaryl-1,2,4-triazine (**B**) was reacted with potassium hydrogen monopersulfate (Oxone) (Scheme 3). The reaction was expected to proceed via steps (iii) and (v) in which leaving group 3-methylsulfonyl group would have to be replaced with various benzylamines in nucleophilic addition reactions to afford 3-benzylamine substituted 1,2,4-triazines.[10] However, the reaction of compound **B** with Oxone did not occur as planned, proceeding via steps (iii) and (iv). Characterization of the purified products by ^{1}H, ^{13}C-NMR, mass spectrometry and X-ray crystallography confirmed the structures of compounds **C** and **D** (Scheme 3 and Figure 2). Subsequently, the reaction of N,2-bis(4-methoxybenzoyl)hydrazine-1-carboxamide (**C**) with various benzylamines yielded (N-benzyl)carbamoylbenzamides **E1-5** (Table 1), which were fully characterized by ^{1}H, ^{13}C-NMR, mass spectrometry and, in the case of **E2**, single crystal X-ray diffraction (Figure 3 and Supplementary material). For the detail of

procedures used for the preparation of compounds **A** and **B**, please refer to our previously published articles.[11,12]

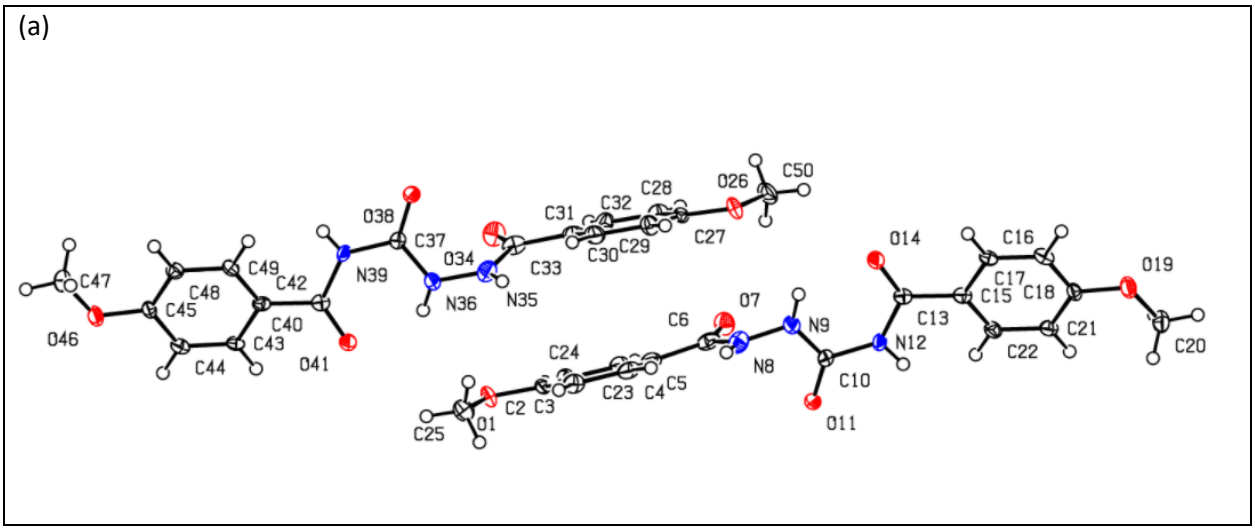


Scheme 3. Synthetic route for the preparation of N-Benzyl-N'-acylureas, **E1-5**. i) thiosemicarbazide, H_2O, EtOH, MW, 130 °C, 20 min. ii) MeI, MeOH, Et_3N, rt. iii) Oxone, THF, H_2O, MeOH, rt. iv) benzylamine deriv., CH_3CN, Et_3N, reflux.

The molecular weights and formulae of N-acylureas **E1-5**, together with their isolation yields (conversion of **B** to **E1-5**), are presented in Table 1. Plausible mechanisms for the reactions to afford **C**, **D** and **E1-5** are illustrated in Schemes 4 and 5. In order to confirm and prove the hypothesis, the starting material 5,6-bis(4-methoxyphenyl)-1,2,4-triazin-3-ol was also treated with Oxone under the same conditions and also produced compounds **C** and **D**.

The production of either the 3-methylsulfonyl or 3-hydroxy derivatives of 5,6-bis(4-methoxyphenyl)-1,2,4-triazin and subsequent conversion to the **C** and **D** products seems feasible

under acidic and oxidative conditions in the presence of Oxone. At the first step, protonation of N1 and N4 atoms of the triazine ring facilitates nucleophilic attack of water at positions C3, C5 and C6 of the triazine ring due to the strong electron withdrawing nature of the 1,4-protonated nitrogen atoms. Subsequently, oxidation of sulfur to sulfonyl and then its replacement as a leaving group by hydroxyl, as long as nucleophilic attack of water occurs at positions C5 and C6, results in the breakdown of the C5-C6 bond of the triazine ring and oxidation to compound **C** (Scheme 4 and Figure 2a). A plausible mechanism for the formation of compound **D** is depicted in Scheme 5. Accordingly, oxidation of the sulfur atom at position 3, and its replacement by a hydroxyl group together with nucleophilic attack of the persulfate oxygen atom at C5 of triazine ring initiates the conversion. This is followed by migration of the 4-methoxyphenyl ring from C5 to the oxygen atom of persulfate and hence release of the sulfate anion. This arrangement leaves the terminal oxygen atom of the persulfate in the structure bearing 4-methoxyphenyl while attached to the C5 of the triazine ring. In the next step, attack of a water molecule at the electrophilic C5 atom results in the 4-methoxy phenol group leaving and the production of compound **D**. Compound D was isolated and purified then characterized by NMR, mass spectrometry and X-ray crystallography (Figure 2b). The production of compounds **E1-5** was accomplished by the reaction of **C** with various benzylamines. The structure of one of the products, **E2**, is discussed below.



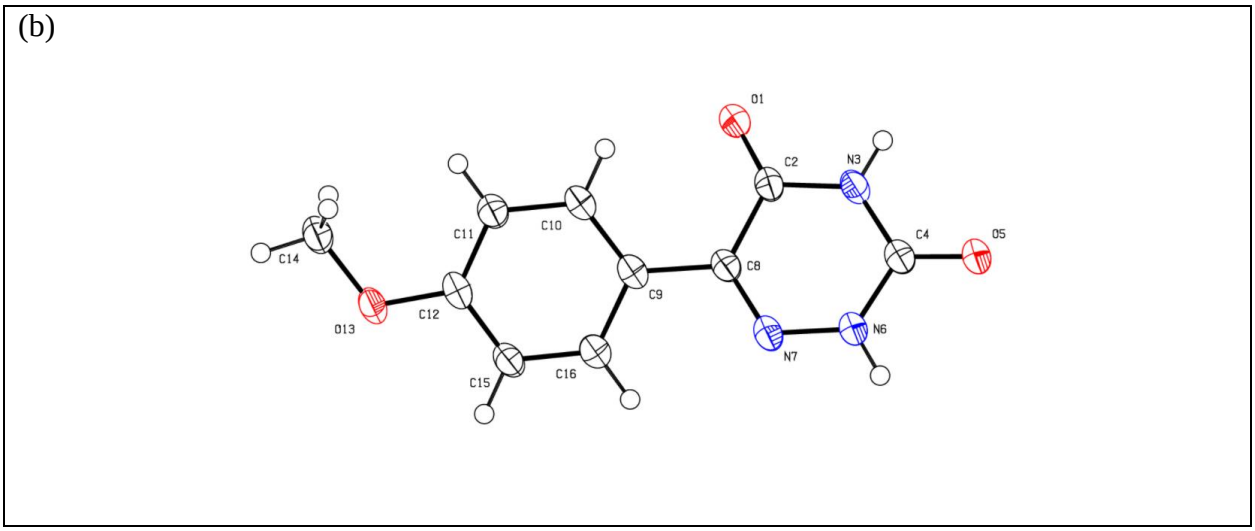
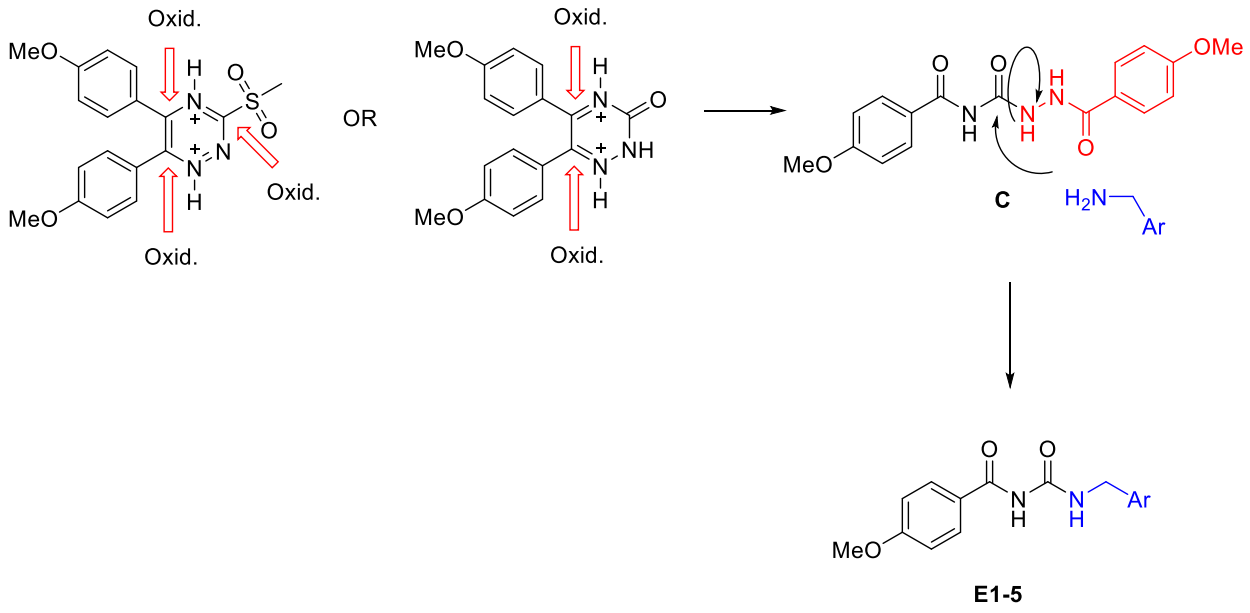
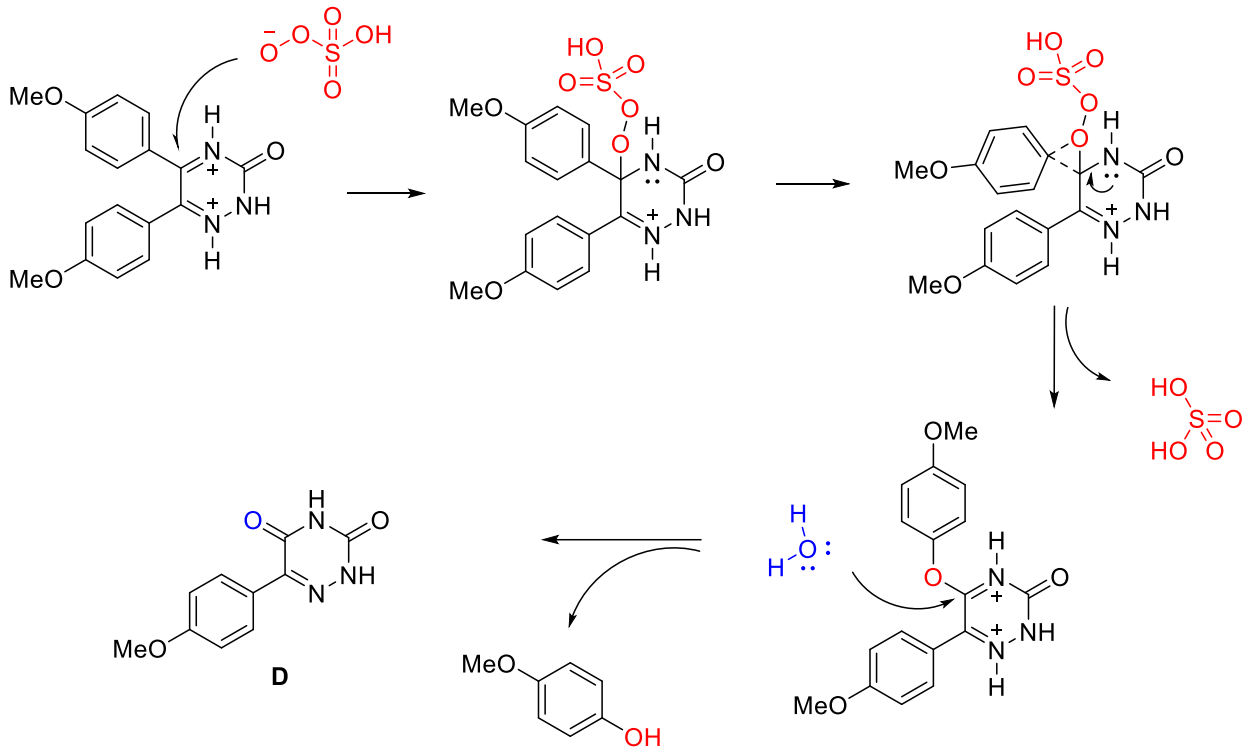


Figure 2. ORTEP structures showing (a) the two molecules of compound **C** in the asymmetric unit (which are held together by a network of H bonding) and (b) the asymmetric unit of compound **D**, as determined by single-crystal X-ray diffraction. Displacement ellipsoids for non-hydrogen atoms are shown at 50% probability level. Crystallographic details are given in Tables S6 and S7 and have Cambridge Crystallographic Data Centre deposit codes CCDC2076143 and CCDC 2076150, respectively.



Scheme 4. Proposed mechanisms for the reactions leading to the formation of Compounds **C** and **E1-5.** Red arrows indicate positions attacked by water and where oxidation occurs.



Scheme 5. Possible mechanism for the formation of compound **D**.

here

Table 1. Details for N-acylureas **E1-E5.**

Compd. code	Ar	Molecular weight	Molecular Formula	Yield% [a]
E1	3-Pyridyl	285	$C_{15}H_{15}N_3O_3$	35
E2	4-Pyridyl	285	$C_{15}H_{15}N_3O_3$	35
E3	Phenyl	284	$C_{16}H_{16}N_2O_3$	45
E4	4-Methoxyphenyl	314	$C_{17}H_{18}N_2O_4$	44
E5	3,4,5-Trimethoxyphenyl	374	$C_{19}H_{22}N_2O_6$	33

[a] Yields are for the conversion of compound **B** to **E1-5** (two steps).

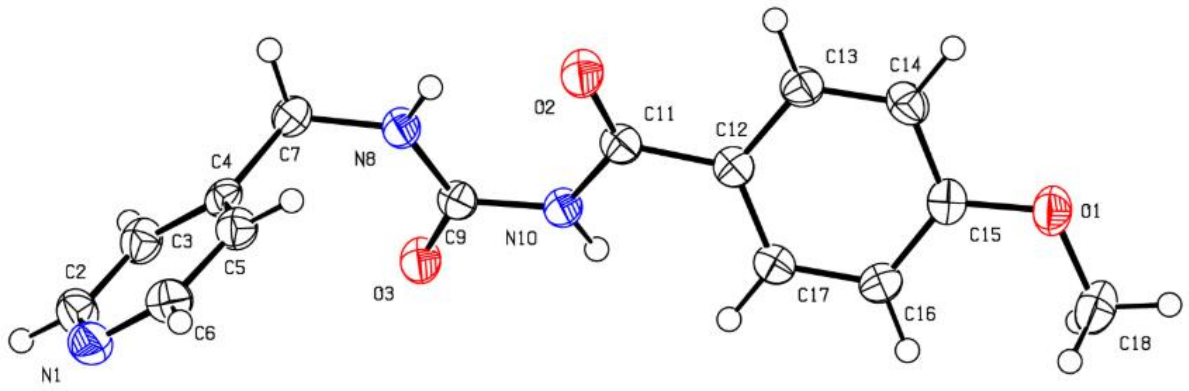


Figure 3. ORTEP structure of the asymmetric unit of compound **E2**, as determined by single-crystal X-ray diffraction, showing the labelling scheme. Displacement ellipsoids for non-hydrogen atoms are shown at 50% probability level (see Tables S1-S5). Cambridge Crystallographic Data Centre deposit code CCDC1853114.

X-ray analysis of a single crystal of compound **E2** showed that there are two molecules of the N-acylurea in the unit cell (Figure 3). The bond lengths and bond angles are as expected for the particular organic groups (Table S3). The angle between the mean planes of the two benzene rings in the molecule is ~ 81°. The molecules pack together as shown in Figure S1. Hydrogen bonding interactions occur between adjacent molecules and run parallel to the *b* axis (N(10) – H(101)…O(3) and N(8) – H(81)…O(2) at 2.8624(16) and 2.9829(16) Å, respectively) (Figure S2 and Table S4). An intramolecular H-bonding interaction (N(8) – H(81)…O(2)) also occurs at 2.6946(16) Å.

In summary, N-Acylurea substructures are becoming attractive and potentially useful scaffolds in medicinal chemistry of drug development projects, especially in peptidomimetic science. The new synthetic method described here should help the development of new N-acylurea derivatives.

Experimental section

General procedure for the preparation of N-acyl ureas (**E1-5**).

To a mixture of N,2-bis(4-methoxybenzoyl)hydrazine-1-carboxamide (**C**) (0.29 mmol, 1 eq) in acetonitrile and triethylamine (1 eq), was added benzylamine derivative (0.32 mmol, 1.1 eq) and the resulting mixture was refluxed for 24-48 hours. The reaction progress was checked by TLC.

After cooling the reaction mixture to room temperature, it was concentrated under vacuum and was chromatographed through silica gel (230-400 mesh) eluting with chloroform/methanol (5%) to give the pure product. Single crystals were prepared by the slow evaporation of dissolved compounds **E1-5** in absolute ethanol. Full characterization data for **E1-5** are provided in the Supplementary Material.

Conflict of interest

Authors declare no conflict of interest.

Acknowledgments

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Supplementary material

Full experimental detail including synthetic routes, ^{1}H and ^{13}C-NMR, Mass spectrometry and X-ray crystallographic data are given in the Supplementary material.

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