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In situ slow release of isocyanates: synthesis and organocatalytic application of *N*-acylureas

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ABSTRACT

A novel, efficient, and operationally simple one-pot synthesis of both, symmetrical and unsymmetrical *N*-acylureas from carboxamides and in situ generated isocyanates (from *N*,*N*-dibromo-*p*-toluenesulfonamide) in the presence of a mild base at rt is reported. The protocol avoids the tedious isolation and purification steps of hazardous isocyanates. The first application of these acylureas to the catalysis through hydrogen bonding is also demonstrated.

N-Acylureas are common building blocks of bioactive molecules, which have potential medical, pharmaceutical, and agrochemical applications.[1] *N*-Acylureas have found widespread use in the field of agrochemicals because of their insecticidal property. Specifically, benzoylureas have proved to be potent insect growth regulators (IGRs),[1c] for example, diflubenzuron (**A**), flufenooxuron (**B**), lufenuron (**C**), and novaluron (**D**) show interfering property in the synthesis of insects exoskeleton formed from chitin (Fig. 1). Several *N*-acylurea derivatives have been found to possess antiinflammatory, hypnotic, analgesic, antitumor, anthelmintic, antifungal, and insecticidal properties and they are attractive groups of compounds in chemical and biological research.[1]

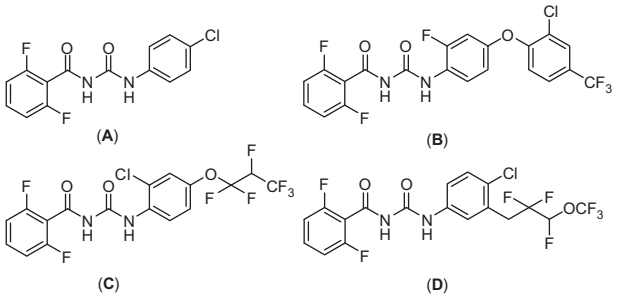
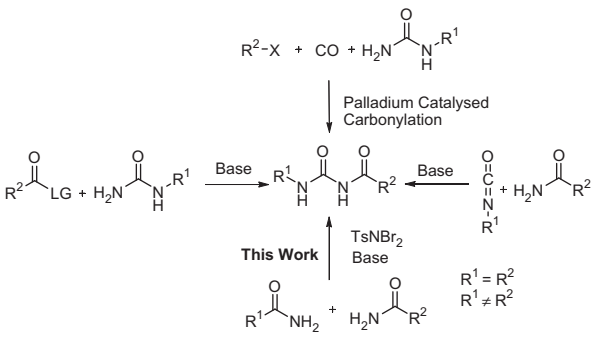


Figure 1. Some biologically active *N*-acylureas.

Various strategies reported for the synthesis of *N*-acylureas include the reaction of substituted ureas with acyl chlorides or acids at an elevated temperature, transition-metal-catalyzed carbonylation, and the reaction between an amide and isocyanate, which is toxic and difficult to isolate (Scheme 1).[2]

Most of the methods available for the synthesis of *N*-acylurea are not satisfactory in terms of reaction time, substrate accessibility, high cost, use of hazardous chemicals, and transition metals. Cost of *N*-acylureas is very high, hence the development of a cost effective and practical synthetic method utilizing easily available starting materials would be welcomed by academia and industry. Considering the above points and our ongoing efforts to develop synthetic processes from easily accessible substrates,[3] we have de-



Scheme 1. Synthesis of *N*-acylureas.

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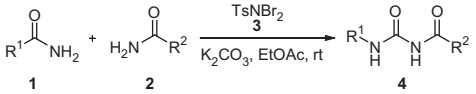
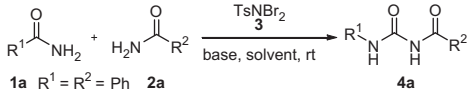


Scheme 2. Synthesis of *N*-acylureas **4**.

Table 1
Optimization of reaction conditions for the synthesis of *N*-acylurea **4a**[a]



Entry	$TsNBr_2$ (equiv)	Base (equiv)	Solvent	Time (h)	Yield[b] (%)
1	1.0	Na_2CO_3 (3)	EtOAc	5	78
2	1.0	Cs_2CO_3 (3)	EtOAc	5	75
3	1.0	K_2CO_3 (3)	EtOAc	5	89
4	1.0	$NaHCO_3$ (3)	EtOAc	5	71
5	1.0	DBU (3)	EtOAc	7	40
6	1.0	DABCO (3)	EtOAc	10	33
7	1.0	Et_3N (3)	EtOAc	10	21
8	1.0	K_2CO_3 (3)	CH_3CN	6	83
9	1.0	K_2CO_3 (3)	DCM	7	75
10	1.0	K_2CO_3 (3)	Toluene	7	81
11	1.0	K_2CO_3 (3)	THF	10	77
12	1.0	K_2CO_3 (3)	Dioxane	6	66
13	2.0	K_2CO_3 (3)	EtOAc	7	89
14	0.7	K_2CO_3 (3)	EtOAc	5	66
15	1.0	K_2CO_3 (2.5)	EtOAc	5	84
16	1.0	K_2CO_3 (3.5)	EtOAc	10	89
17	—	K_2CO_3 (3)	EtOAc	5	—
18	1.0	—	EtOAc	5	—

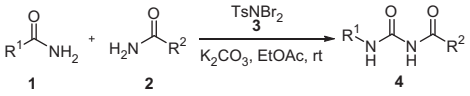
[a] For experimental procedure, see Ref. [6].
[b] Isolated yield of purified product **4a**.

vised an efficient protocol for the synthesis of *N*-acylureas. Based on the fact that in Hofmann bromamide reaction a small amount of *N*,*N*-acylurea is also formed in addition to primary amine as the major product, we hypothesized that a slow release of the isocyanate intermediate in the reaction mixture, would afford *N*-acylureas as the main product. *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$), first discovered by Kharasch,[4a] has been utilized for carrying out a variety of organic transformations.[4] Recently, Phukan et al. have developed a method for the synthesis of carbamates via isocyanates generated in situ by the reaction of amides using $TsNBr_2$.[4i] Thus, for the present study, we examined *N*,*N*-dibromo-*p*-toluenesulfonamide and found that it worked well. Herein, we report the first synthesis of *N*-acylureas **4** using carboxamides **1**, **2**, and *N*,*N*-dibromo-*p*-toluenesulfonamide **3** in the presence of K_2CO_3 in ethyl acetate at rt (Scheme 2).

The general procedure was first optimized with respect to solvents, bases, and amount of *N*,*N*-dibromo-*p*-toluenesulfonamide using benzamide (**1a**) as a model substrate for the synthesis of a representative N-acylurea **4a** (Table 1). We initiated our investigation by optimization of bases and found that K_2CO_3 was the best among Na_2CO_3, Cs_2CO_3, $NaHCO_3$, DBU, DABCO, and Et_3N (Table 1, entry 3). Then we focused on the quantitative optimization of K_2CO_3 and *N*,*N*-dibromo-*p*-toluenesulfonamide. It was found that the best yield of *N*-acylurea **4a** was obtained with 3.0 equiv of K_2CO_3 (Table 1, entry 3). The yield of **4a** decreased in the presence of 2.5 equiv of K_2CO_3 in comparison to 3.0 equiv of K_2CO_3 (Table 1, entry 15). In the presence of 3.5 equiv of K_2CO_3 the yield of **4a** did not change even when the reaction time was extended up to 10 h (Table 1, entry 16). The optimum loading of *N*,*N*-dibromo-*p*-toluenesulfonamide **3** for the reaction was found to be 1.0 equiv (Table 1, entry 3). The use of 2.0 equiv of **3** did not increase the yield of **4a** but on using 0.7 equiv of **3**, the yield was considerably decreased (Table 1, entries 13 and 14). For comparison purposes, the reaction was also performed in various solvents, and EtOAc was found to be the best in terms of the yield and reaction time (Table 1, entry 3).

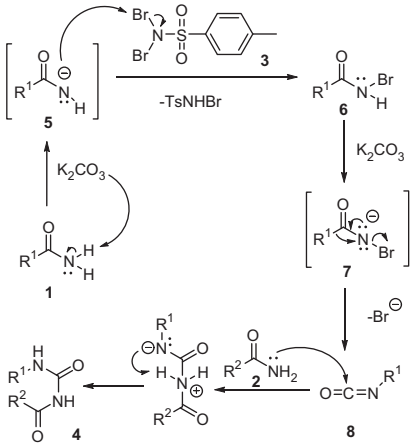
After optimizing the reaction conditions, the process was extended to a variety of aromatic carboxamides and a wide range

Table 2
Synthesis of *N*-acylureas **4**[a]



Entry	R^1	R^2	Product[b]	Time (h)	Yield[c] (%)
1	C_6H_5	C_6H_5	**4a**	5	89
2	4-ClC_6H_4	4-ClC_6H_4	**4b**	6	94
3	3-ClC_6H_4	3-ClC_6H_4	**4c**	6	84
4	2-ClC_6H_4	2-ClC_6H_4	**4d**	5	86
5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4e**	6	87
6	3-$MeOC_6H_4$	3-$MeOC_6H_4$	**4f**	6	81
7	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	**4g**	5	94
8	4-BrC_6H_4	4-BrC_6H_4	**4h**	6	92
9	2-BrC_6H_4	2-BrC_6H_4	**4i**	5	89
10	4-MeC_6H_4	4-MeC_6H_4	**4j**	5	92
11	3-MeC_6H_4	3-MeC_6H_4	**4k**	6	87
12	2-MeC_6H_4	2-MeC_6H_4	**4l**	5	90
13	$C_6H_5(CH_2)_2$	$C_6H_5(CH_2)_2$	**4m**	6	82
14	C_6H_5	CH_3	**4n**	5	78[d]
15	C_6H_5	C_2H_5	**4o**	6	76[d]
16	4-ClC_6H_4	CH_3	**4p**	6	73[d]
17	4-ClC_6H_4	C_2H_5	**4q**	6	67[d]

[a] For experimental procedure, see Ref. [6].
[b] All are new compounds except **4a**.[2b]
[c] Isolated yield of purified product **4**.
[d] In addition to unsymmetrical *N*-acylureas **4m**, **4n**, **4o**, and **4p**, the corresponding symmetrical *N*-acylureas **4a**, **4b**, were isolated in 5%, 6%, 6%, and 8% yield.



Scheme 3. A plausible mechanism for the formation of *N*-acylureas **4**.

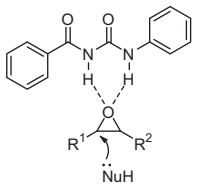
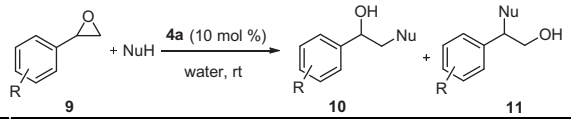


Figure 2. H-bonding organocatalysis of *N*-acylureas **4**.

Table 3
N-Acylurea catalyzed ring-opening of styrene oxide in aqueous media[a]

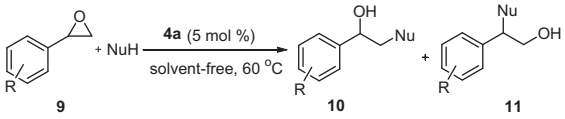


9 10 11

Entry	R	NuH	Time (h)	Product	Yield[b] (%)	Regioselectivity[c] **10**:**11**
1	H	$PhNH_2$	22	**10a**:**11a**	90	20:80
2	H	PhSH	22	**10b**:**11b**	78	22:78
3	H	PhOH	22	**10c**:**11c**	75	25:75
4	Cl	$PhNH_2$	30	**10d**:**11d**	82	22:78
5	Cl	PhSH	30	**10e**:**11e**	73	23:77
6	Cl	PhOH	30	**10f**:**11f**	70	25:75
7	Me	$PhNH_2$	18	**10g**:**11g**	88	21:79
8	Me	PhSH	18	**10h**:**11h**	79	24:76
9	Me	PhOH	18	**10i**:**11i**	75	26:74
10	H	$PhNH_2$	22	**10a**:**11b**	—	—[d]

[a] For experimental procedure, see Ref. [7].
[b] Isolated yield of purified product.
[c] As determined by ^{1}H NMR.
[d] The reaction was performed in the absence of catalyst **4a**.

Table 4
N-Acylurea catalyzed solvent-free ring-opening of styrene oxide[a]



9 10 11

Entry	R	NuH	Time (h)	Product	Yield[b] (%)	Regioselectivity[c] **10**:**11**
1	H	$PhNH_2$	2.5	**10a**:**11a**	96	12:88
2	H	PhSH	2.5	**10b**:**11b**	80	20:80
3	H	PhOH	2.5	**10c**:**11c**	78	24:76
4	Cl	$PhNH_2$	3.4	**10d**:**11d**	90	13:87
5	Cl	PhSH	4.0	**10e**:**11e**	76	22:78
6	Cl	PhOH	3.5	**10f**:**11f**	70	25:75
7	Me	$PhNH_2$	0.4	**10g**:**11g**	93	10:90
8	Me	PhSH	0.5	**10h**:**11h**	75	16:84
9	Me	PhOH	0.4	**10i**:**11i**	74	20:80
10	H	$PhNH_2$	18	**10a**:**11b**	82	30:70[d]

[a] For experimental procedure, see Ref. [8].
[b] Isolated yield of purified product.
[c] As determined by ^{1}H NMR.
[d] The reaction was performed in the absence of catalyst **4a**.

of symmetrical *N*-acylureas **4** were readily synthesized in excellent yields. Results are summarized in Table 2, entries 1–12. After being successful in the case of aromatic carboxamides, the procedure was also tried with aliphatic carboxamides. It was observed that acetamide and propionamide failed to give the corresponding symmetrical *N*-acylureas **4** and were recovered as such even after 15 h. However, 3-phenylpropanamide afforded the corresponding symmetrical *N*-acylurea in good yield (Table 2, entry 13). Further, the process was extended to the synthesis of unsymmetrical *N*-acylureas using a mixture of aromatic and aliphatic carboxamides, the corresponding unsymmetrical *N*-acylureas **4** were readily synthesized in good yields as the sole product derived from the aryl isocyanate and acetamide or propionamide (Table 2, entries 14–17). This is probably because acetamide and propionamide failed to form the corresponding isocyanate under the optimized reaction conditions. The important feature of this procedure is the compatibility of the reaction conditions with a broad range of functional groups including ether, nitro, and halo groups.

On the basis of the above experimental results, a plausible mechanism for the formation of *N*-acylureas **4** is depicted in Scheme 3. Initially, the non-nucleophilic base K_2CO_3 deprotonates the NH_2 group of amide **1** to generate the anion **5** which subsequently picks up Br^+ from $TsNBr_2$ resulting in the facile formation of *N*-bromamide **6**. Again, K_2CO_3 promoted proton loss from **6** generates bromoamide anion **7** which undergoes the Hofmann rearrangement to form the corresponding isocyanate **8.** After the formation of isocyanate, it is immediately attacked by the NH_2 group of carboxamide to form the *N*-acylurea **4**.

The H-bonding organocatalytic ability of ureas and thioureas is well established,[5] which led us to investigate the catalytic activity of the synthesized *N*-acylurea **4** in the nucleophilic ring-opening of epoxides. Interestingly, it was observed that *N*-acylurea **4a** served as a better H-bonding organocatalyst than the earlier reported ureas[5] in terms of time for the epoxide ring opening with various nucleophiles. To the best of our knowledge this is the first report on using an *N*-acylurea as a H-bonding organocatalyst (Fig. 2). We commenced our study with the reaction of styrene oxide with different nucleophiles in water at rt using 10 mol % of representative *N*-acylurea **4a**. *N*-Acylurea was found to be an efficient regioselective catalyst for the ring-opening of epoxides with various nucleophiles and the results are summarized in Table 3, entries 1–9. In the absence of catalyst **4a**, the products **10a** and **11a** were not formed (Table 3, entry 10).

Next, we studied the catalytic activity of *N*-acylurea **4a** under solvent-free conditions. At 60 °C under solvent-free conditions, catalytic activity of *N*-acylurea was increased in comparison to water and the results are summarized in Table 4, entries 1–9. In the absence of catalyst **4a**, the products **10a** and **11a** were formed in lower yield and regioselectivity (Table 4, entry 10).

In conclusion, we have developed a novel, efficient, and operationally simple one-pot synthesis of *N*-acylureas using carboxamides and in situ generated isocyanates (from *N*,*N*-dibromo-*p*-toluenesulfonamide) in the presence of a mild base at rt. The protocol avoids the isolation and purification steps of hazardous isocyanates, which makes it a superior alternative for the synthesis of *N*-acylureas. The synthetic potential of the synthesized *N*-acylureas has been demonstrated by their effective catalytic activity for the nucleophilic ring-opening of epoxides.

Acknowledgments

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6. *General procedure for the synthesis of N-acyl-N′-arylureas 4:* To a solution of carboxamide 1 (1 mmol) and 2 (1 mmol) in EtOAc (12 mL), *N*,*N*-dibromo-*p*-toluenesulfonamide 3 (1 mmol) and K_2CO_3 (3 mmol) were added and the mixture was stirred under nitrogen at room temperature for 5–6 h (Table 2). After completion of reaction (monitored by TLC), water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a mixture of EtOAc–*n*-hexane (1:9) as eluent to afford an analytically pure product.
   Characterization data of representative compounds.
   Compound **4a**[2]: White solid, yield 89%, mp 189−191 °C (lit. mp: 191−193 °C),2 ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.92 (s, 1H), 9.52 (s, 1H), 8.04–8.02 (m, 2H), 7.66–7.58 (m, 3H), 7.55–7.51 (m, 2H), 7.39–7.34 (m, 2H), 7.17–7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.61, 150.98, 137.53, 132.92, 132.14, 128.95, 128.44, 128.19, 123.65, 120.32. EI-MS (*m*/*z*) 240 (M^+). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66%. Found: C, 69.71; H, 5.38; N, 11.54%. These observed spectral and elemental analyses' data compare quite favourably to those reported in the literature.[2] Compound **4n**: White solid, yield 78%, mp 182−184 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.63 (s, 1H), 9.97 (s, 1H), 7.53–7.51 (m, 2H), 7.35–7.31 (m, 2H), 7.15–7.11 (m, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.99, 148.06, 139.68, 128.98, 128.12, 121.85, 22.04, EI-MS (*m*/*z*) 178 (M^+). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72%. Found: C, 60.98; H, 5.83; N, 15.46%.
7. *General procedure for the ring-opening of styrene oxide (**9**) in water:* A mixture of styrene oxide 9 (1 mmol), nucleophile NuH (1 mmol), and *N*-acylurea **4a** (0.1 mmol) was stirred in water (2 mL) at room temperature for 18–30 h (Table 3). After completion of reaction (monitored by TLC), water (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a mixture of EtOAc–*n*-hexane (1:19) as eluent to afford an analytically pure product.
8. *General procedure for the solvent-free ring-opening of styrene oxide:* A mixture of styrene oxide 9 (1 mmol) and nucleophile NuH (1 mmol) and *N*-acylurea **4a** (0.05 mmol) was stirred under solvent-free condition at 60 °C for 0.4–4.0 h (Table 4). After completion of reaction (monitored by TLC), water (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a mixture of EtOAc–*n*-hexane (1:19) as eluent to afford an analytically pure product. Compound **10c**[9]: White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.85 (s, 1H), 3.98–4.10 (m, 1H), 4.16–4.18 (m, 1H), 5.11–5.18 (m, 1H), 6.96–7.02 (m, 3H), 7.29–7.48 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.43, 139.78, 129.63, 128.60, 128.26, 126.39, 121.36, 114.73, 73.38, 72.67. EI-MS (*m*/*z*) 214 (M^+). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59%. Found: C, 78.31; H, 6.85%. Compound **11c**[9]: White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.27–2.31 (m, 1H), 3.80–3.92 (m, 1H), 3.95–4.02 (m, 1H), 5.29 (dd, *J* = 8.3, 3.9, 1H), 6.89–6.94 (m, 3H), 7.20–7.41 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.86, 137.91, 129.49, 128.79, 128.19, 126.36, 121.31, 115.98, 81.22, 67.66. EI-MS (*m*/*z*) 214 (M^+). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59%. Found: C, 78.24; H, 6.89%.

9. Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 726.