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An unexpected reaction to methodology: an unprecedented approach to transamidation†

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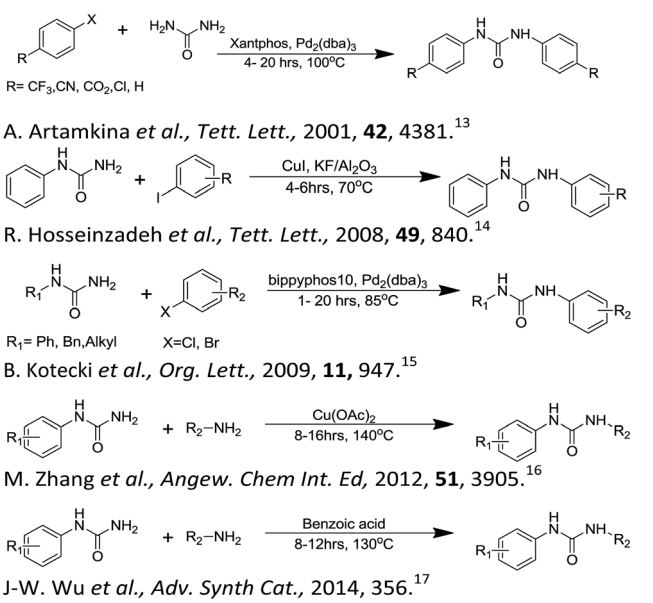
This report describes an unprecedented protocol for the synthesis of *N*,*N*′-substituted ureas using a cross-coupling method. Mono substituted ureas were modified by an economically viable and simple method using commercially available isocyanates and sodium hydride as the reagents. In addition, the method involves no expensive metal complexes or catalysts and all reactions are carried out at room temperature. Furthermore, both symmetrical and asymmetrical ureas were successfully obtained in single step reactions with reasonable yields.

Urea, *N*-substituted symmetric and asymmetric ureas are a most important class of compounds which have found extensive applications in agriculture,[1] are medicinally important and are found in natural products.[2] Many substituted ureas are also known as potent HIV-1 protease inhibitors.[3] Many classical procedures and catalytic transformations have been reported in the literature for urea synthesis. Isocyanate[4] and phosgene[5] are the most predominant reactants used in the traditional methods although phosgene surrogates have been developed to replace the gaseous phosgene.[6] Ureas are also produced using activated carbamates,[7] carbonates,[8] carbonyldiimidazole,[9] carbon monoxide[10] and carbon dioxide[11] at higher temperatures.

Although a significant number of cross-coupling methodologies have been developed for *N*-arylation,[12] few have been applied to the *N*-arylation of urea and substituted ureas[13–19] (Scheme 1). Very recently ruthenium catalyzed urea synthesis also reported by Kim *et al.*[20] Nevertheless, none of these procedures provide a general and practical synthetic method for the preparation of *N*-aryl or *N*-heteroaryl ureas. Problem lies with above prescribed cross-coupled methods are less in yield, long reaction time and usage of expensive metal complexes and recovery of the same from the reaction mixture, which often results in metal contamination of in the product.

In our research on the development of methodologies in organic synthesis,[21] we have developed a simple, unprecedented and unusual protocol for *N*-substituted ureas.

We were trying to prepare one of the impurities (E) of iprodione, which can be prepared theoretically by reacting 3,5-dichlorophenylurea (**1a**) with isopropyl isocyanate under basic conditions (Scheme 2). However, when we conducted the reaction, the starting material was consumed as expected but analysis showed that the expected product was not obtained; instead we formed 1-(3,5-dichlorophenyl)-3-isopropylurea (**3a**) as an unexpected product. When the same methodology was reapplied, we confirmed the generality and viability of the



Scheme 1 Previous work on urea synthesis by cross-coupling methods.

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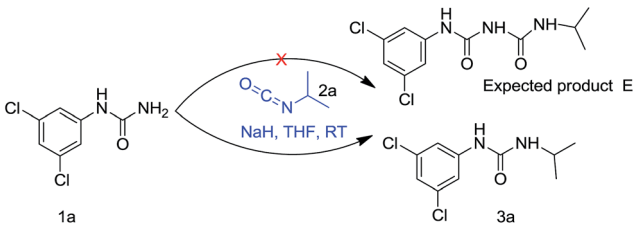


Scheme 2 Unexpected result from the reaction of 3,5-dichlorourea (**1a**) with isopropyl isocyanate.

method for *N*-substituted ureas and developed a working protocol.

In order to obtain the optimal reaction conditions, 3,5-dichlorourea (**1a**) was considered as a model substrate, and several bases and solvents were screened at different temperatures (Scheme 3). The obtained results are tabulated in Table 1.

Several solvents were screened to check their effect on yield. THF was found to be the best among the solvents employed (Table 1, entries 1–4), even though DMF did increase the yield relative to MTBE and dioxane. Knowing the importance of basicity, organic and inorganic bases were selected for the reaction and sodium hydride was found to be the best (Table 1, entries 3, 5–7). Temperature is a critical parameter in the reaction; at temperatures lower than room temperature (RT), the reaction did not reach completion, resulting in a very low yield, while at temperatures higher than RT, no significant improvement in the yield was observed, which might be due to the decomposition of the product formed (Table 1, entries 8–14). An increase in the reaction time did not make any difference to the yields of the reaction (Table 1, entries 15–17). However, upon decreasing the amount of the base NaH from 1.0 eq. to 0.5 eq., the yield of the product was decreased (Table 1, entry 18). No significant improvement in the yield was observed when NaH was increased from 1.0 eq. to 1.5 eq. or 2.0 eq. (Table 1, entries 19 and 20).

The developed method was utilized to explore its tolerance to different functional groups. Thus, different ureas and isocyanates (Scheme 4) were reacted under optimized conditions, and the obtained results are tabulated in Table 2.

Initially, isopropyl, *tert*-butyl and phenyl isocyanates were treated with dichlorophenylurea, and the corresponding *N*,*N*′-substituted ureas (entries **3a–3c**) were formed without affecting the chloro groups. Phenylureas and 4-methoxy phenylureas were also obtained in good yields from the corresponding substituted ureas (entries **3d–3i**) without any major additional products. Aliphatic ureas reacted similarly, and simply converted to *N*,*N*′-substituted ureas (entries **3j–3l**). In order to check

Table 1 Optimization of base, solvent and temperature for the synthesis of **3a**[a]

Entry	Solvent	Base (eq.)	Temp. (°C)	Time (h)	Yield[b] (%)
1	MTBE	NaH (1.0)	RT	2	20
2	THF	NaH (1.0)	RT	2	83
3	Dioxane	NaH (1.0)	RT	2	25
4	DMF	NaH (1.0)	RT	2	66
5	THF	TEA (1.0)	RT	2	—
6	THF	Pyridine (1.0)	RT	2	—
7	THF	K_2CO_3 (1.0)	RT	2	—
8	THF	NaH (1.0)	10	2	30
9	THF	NaH (1.0)	20	2	43
10	THF	NaH (1.0)	30	2	80
11	THF	NaH (1.0)	40	2	70
12	THF	NaH (1.0)	50	1	48
13	THF	NaH (1.0)	60	1	30
14	THF	NaH (1.0)	70	1	22
15	THF	NaH (1.0)	RT	4	80
16	THF	NaH (1.0)	RT	12	75
17	THF	NaH (1.0)	RT	24	70
18	THF	NaH (0.5)	RT	2	48
19	THF	NaH (1.5)	RT	2	86
20	THF	NaH (2.0)	RT	2	85

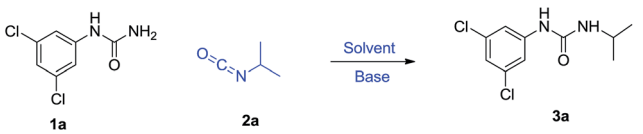
[a] Reactions were performed with 1 mmol of **1a** and 1.2 mmol of isocyanate (**2a**). [b] Yields relate to isolated chromatographically purified compounds.

the effect on reactivity of different positions of the methyl group using dimethylphenylurea substrates, we synthesized **3m–3p**. It was clear that 2,6-dimethylphenylurea yields less compared to 2,4, 3,4 or 3,5-dimethylphenylureas, which might be due to steric hindrance from the methyl groups.

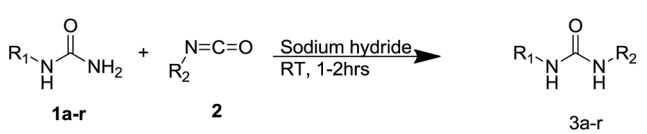
Both electron-rich and electron-deficient substrates gave similar yields, and various functionalities were tolerated including halo, ether, methyl and aliphatic groups. These examples clearly demonstrate the utility of the protocol for wider applicability. The products were obtained in reasonable purity by column chromatography followed by a simple aqueous workup.

Interestingly, to study the mechanism of the reaction, we tried different supporting reactions (Scheme 5), but we have failed to conclude the exact mechanism used.

Initially urea was treated with sodium hydride, to find out whether urea was converting to aniline (A) *in situ*, and then reacting with isocyanate to yield the urea product, but even after 24 h there was no change in the starting material, which indicates that there was no formation of aniline in the reaction. Next thiourea was treated with isocyanate (B), and the substituted thiourea was formed, revealing that the reaction was taking place at the *N*′-nitrogen moiety. Finally the urea substrate was

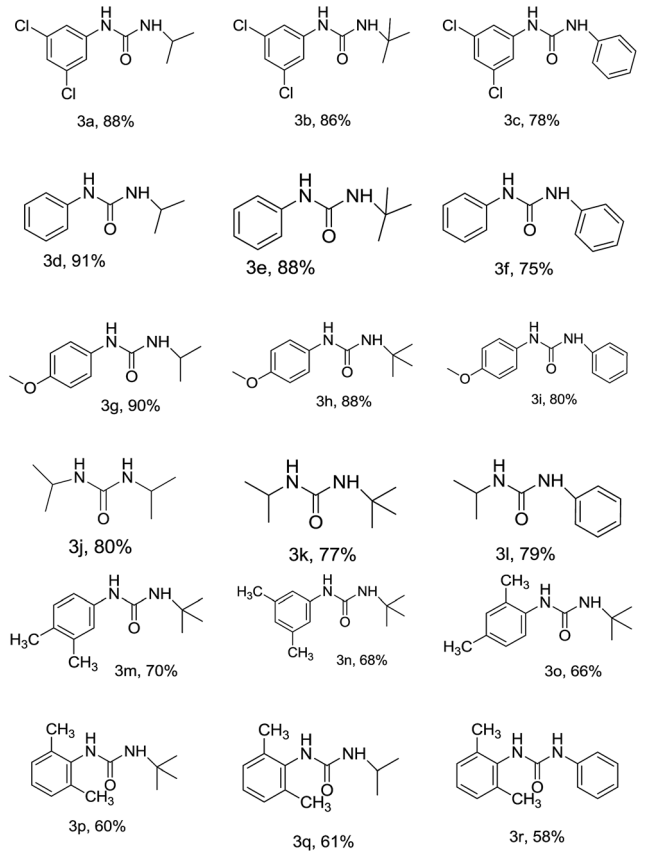


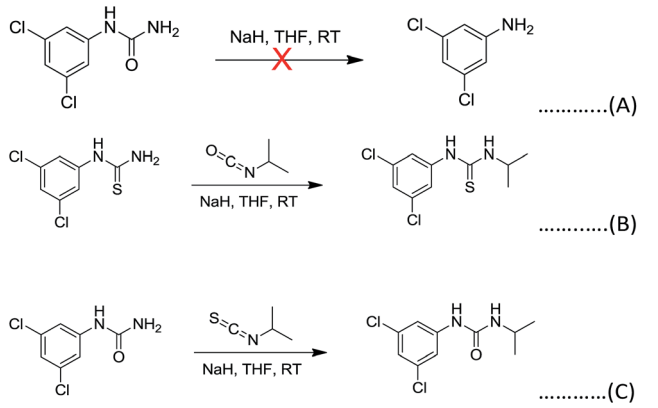
Scheme 3 Reaction of 3,5-dichlorourea (**1a**) with isopropyl isocyanate with different bases, solvents and temperatures.



Scheme 4 Symmetrical and asymmetrical ureas from sodium hydride and isocyanate.

Table 2 Yields of *N,N′*-substituted ureas from different urea substrates





Scheme 5 Supporting reactions to explore different reaction mechanisms.

treated with thioisocyanate (C) and the product formed was a urea instead of a thiourea. This clearly indicated that the newly formed amide carbonyl originated from the urea and not from the isocyanate part, but we failed to draw a conclusion on the exact mechanism.

In summary, we have reported the straightforward synthesis of *N,N′*-substituted ureas from the corresponding mono substituted urea substrates. The key advantages of this method are the mild reaction conditions, the ambient reaction temperature, the use of inexpensive sodium hydride, the exceptional functional group tolerance and the good-to-excellent yields. We are convinced that this procedure is, and will be, of significant value for the synthesis of a variety of amides which are significant in organic and medicinal chemistry. A mechanism study using labelled starting materials is in progress.

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