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COMMUNICATION

Iron(III) catalysed synthesis of unsymmetrical di and trisubstituted ureas – a variation of classical Ritter reaction†

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An application of the classical Ritter reaction for the synthesis of unsymmetrical di and trisubstituted ureas catalyzed by $FeCl_3$ is described. The protocol is of significant interest in view of the easy availability of precursors, mild reaction conditions employed and interestingly its applicability for the alkylation of alcohols capable of forming stable carbocationic intermediates even to the sterically hindered moieties.

Urea functional groups have received considerable diligence due to its wide range of applications in agriculture as agrochemicals, pharmaceutical drugs, petrochemicals, in biology as well as in materials science.[1] They also serve as important intermediates and organocatalysts in organic synthesis.[2] Recent literature cited a few examples of ureas as potent HIV-1 protease inhibitors, p38 MAP kinase inhibitors for the treatment of inflammatory diseases and peptidomimetics with increased metabolic stability.[3,4]

Several methods have been developed for the synthesis of unsymmetrically substituted ureas (Fig. 1). Curtius rearrangement of acyl azides into isocyanates and their further reaction with amine is a well known route for the synthesis of urea.[5] Diphenylphosphoryl azide (DPPA) is the reagent of choice as it allows the direct conversion of carboxylic acids into ureas through Curtius rearrangement in one pot.[6] Besides this, Hoffmann[7] and Lossen[8] rearrangements have also been explored for the synthesis of urea starting from amide and hydroxamic acid respectively. A number of carbonylating reagents[9] were developed including phosgene,[10] triphosgene[11] for the synthesis of title molecules but their preparation suffers inherent limitations. Many carbamates,[12] carbonates,[13] formamides[14] were also developed to serve as a source for the generation of isocyanate which were the active intermediates for the preparation of urea. In addition, carbodiimides[15] on hydrolysis exclusively yields substituted ureas. Other approaches include the oxidative carbonylation of amine with CO in presence of transition metal catalysts[16] or the direct carbonylation of amine by CO_2.[17] Thus, owing to the vast diversity of synthetic applications of ureas it is desirable to augment a simple, safer and an alternative protocol for their synthesis.

In the ongoing studies,[18] we were employing glycosyl cyanamides for the preparation of guanidinoglycosides. During the course of the work, we realized that cyanamides[19] resemble nitriles in reactivity. In addition, J. Anatol *et al.*[20] described the synthesis of acyl and sulfonyl ureas from the corresponding acyl and sulfonylcyanamides. However, their attempt to synthesize substituted ureas from the corresponding cyanamides and *t*-butyl alcohol under reflux condition, in the presence of strong acids such as conc. H_2SO_4 and HCl resulted in very low yields of desired ureas. Thus we started to investigate a simple, mild and an alternative protocol for the synthesis of unsymmetrical di and trisubstituted ureas through a variation of Ritter's reaction.

Ritter's reaction[21] is the classical reaction for the C–N bond formation *i.e.*, amidation of alcohols or alkenes with nitrile in the presence of a Lewis acid.[22,23] Recently, iron catalysis has been considered as an alternative not only because of its lower toxicity and cost compared to other metals but also because it possesses some useful properties which have been utilized in many transformations.[24] Iron catalysed C–C, C–N and C–O bond forming reactions have recently been developed.[25] In the

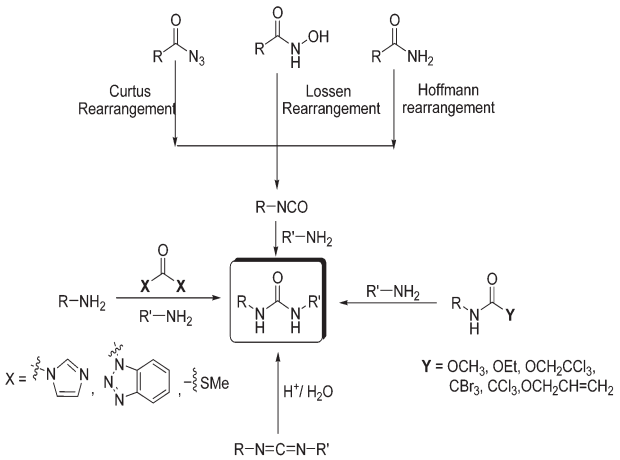

Fig. 1 Schematic representation of various routes reported in the literature for the synthesis of unsymmetrical *N,N'*-disubstituted ureas.

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†Electronic supplementary information (ESI) available: ^1H spectra of **2h**, **2j**, ^1H and ^{13}C NMR spectra of **4a–d**, **4f–k**, **4m**, **4o**, **4r**, **4s** and HRMS spectra of **4e**, **4l**, **4n**, **4p** and **4q**. See DOI: 10.1039/c2ob06916d

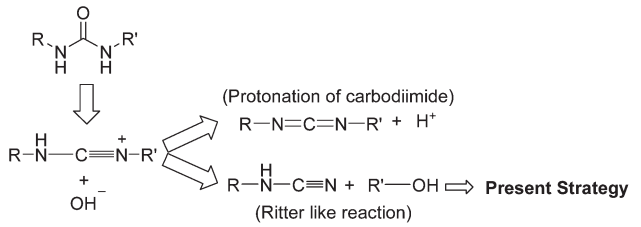
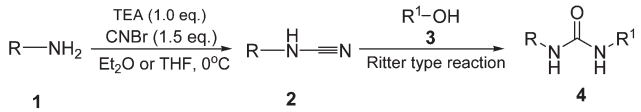


Fig. 2 Retro-synthetic route for the synthesis of unsymmetrical substituted urea.



Scheme 1 Synthesis of unsymmetrical substituted urea through a variation of Ritter reaction.

present context the high Lewis acidity and catalytic activity of $FeCl_3$ towards benzyl and allyl alcohols[26] render us to investigate its use for urea preparation.

The following mechanistic analysis revealed to us the suitability of Ritter's reaction for the synthesis of unsymmetrical ureas from cyanamides and alcohols (Fig. 2).

The utility of Ritter's reaction was not much explored other than for amide bond formation. In view of the above mechanistic analysis, we sought to synthesize ureas from the cyanamides and readily available alcohols which form stable carbocations as starting materials through a variation of the Ritter reaction, wherein the cyanamide serves as the nitrile source (Scheme 1). The cyanamide (**2**) precursors for the present protocol were prepared through a simple route using CNBr in diethyl ether/tetrahydrofuran (THF) as a solvent under mild conditions in the presence of 1.0 eq. of triethylamine (TEA) to scavenge HBr released in the reaction.[27] The reaction is simple, mild and straight forward in yielding desired cyanamides in excellent yields.

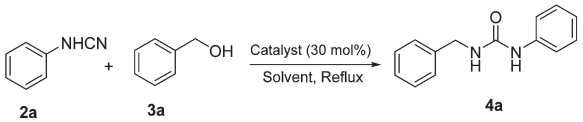
Initially, benzyl alcohol (**3a**) and phenylcyanamide (**2a**) were chosen as substrates to screen the optimized conditions. The results are summarized in Table 1.

Various Lewis acids and solvents were examined, among which $FeCl_3$ in dichloroethane (DCE) proved advantageous in affording good yield (86%) of desired urea (**4a**).

The reaction yield mainly depended on the solvent used (Table 1). DCE and dichloromethane (DCM) were found to be the most effective solvents in terms of reaction duration and yield. The yield was lower with coordinating solvents such as THF and acetonitrile. Thus, we had chosen DCE as the solvent for further work. It has been previously observed that in the presence of a catalytic amount of Lewis acid (in this case $FeCl_3$), benzyl alcohols were rapidly converted into dibenzyl ether (**A**) by eliminating water.[28]

Presumably in the presence of nucleophile *i.e.*, cyanamide, the ether is polarized by $FeCl_3$ and generates an incipient benzylic carbocation. Further the reaction proceeds by the electrophilic addition of thus formed carbocation to the cyanamide. This results in the formation of nitrilium ion, which is then

Table 1 Screening of catalysts and solvents for optimizing the reaction condition



Entry	Catalyst	Solvent	Time (h)	Yield[a] (%)
1	$BF_3{\cdot}Et_2O$	DCM	6	33
2	$AlCl_3$	DCM	6	24
3	$FeCl_3$	DCM	6	68
4	$FeCl_3$	DCE	4.5	86
5	$FeCl_3$	THF	6	43
6	$FeCl_3$	CH_3CN	6	39

[a] Isolated yield under laboratory conditions.

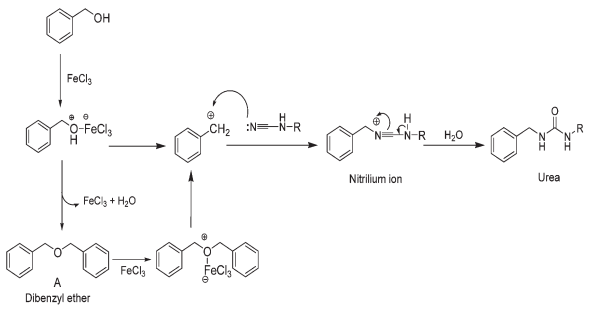


Fig. 3 Plausible reaction pathway for the benzyl substituted urea *via* dibenzyl ether formation.

hydrolysed by H_2O (which is being generated during ether formation) and affords the final product (Fig. 3). In one of the experiments, dibenzyl ether was isolated and confirmed by NMR.

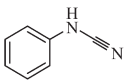
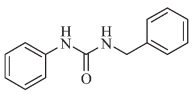
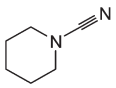
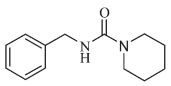
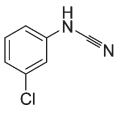
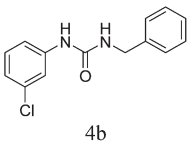
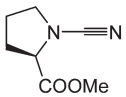
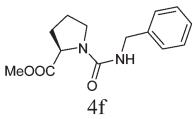
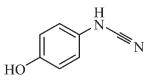
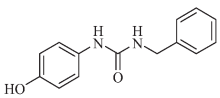
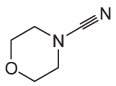
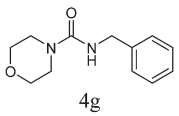
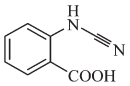
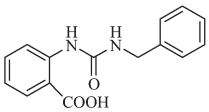
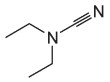
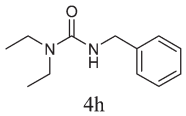
Also the synthesis of **4a** was undertaken employing dibenzyl ether as precursor under optimized Ritter condition. The reaction proceeded well in affording **4a** in quantitative yield. The efficacy of the protocol was further exemplified using benzyl alcohol and variety of amines *i.e.*, precursors for cyanamides (Table 2).

Next we turned our attention to the synthesis of *t*-butyl ureas (Scheme 2). Unfortunately, when *t*-butyl alcohol (**3b**) and phenylcyanamide (**2a**) were employed under the optimized reaction conditions poor yield was observed. In order to increase the yield, a 0.5 eq. of acetic acid was used which assist by forming *t*-butylacetate, a better source of carbocation which further participates in the reaction yielding urea (**4i**) with much ease compared to its alcohol counterpart.[29] Thus in the presence of $FeCl_3$ and AcOH, *t*-butyl ureas were obtained in good to excellent yields as summarized in Table 3.

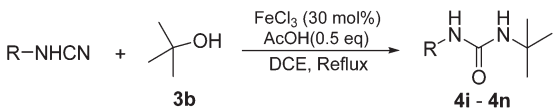
In the next part of the work, other alcohols such as diphenylmethanol (**3c**), 1-phenylethanol (**3d**) and allyl alcohol (**3e**) furnished the corresponding ureas in good to excellent yields (Table 4).

The mechanism for the synthesis of *t*-butyl and allyl urea presumably involves the formation of stable carbocation (*t*-butyl and allylic cation respectively), as in case of a typical Ritter's reaction mechanism.

Table 2 List of benzyl substituted ureas synthesized through benzyl alcohol

Sl. no.	Cyanamide (2)	Urea (4)[a]	Yield[b] (%), Reaction time (h)	M.P. (°C), Obsd (Lit.)	Sl. no.	Cyanamide (2)	Urea (4)[a]	Yield[a] (%), Rean. time (h)	M.P. (°C), Obsd (Lit.)
1	 2a	 4a	86 (4.5)	176–178 (175–176)	5	 2e	 4e	79 (5)	103–104 (102)
2	 2b	 4b	80 (4)	187–189	6	 2f	 4f	71 (5)	227–230
3	 2c	 4c	74 (6)	197–198	7	 2g	 4g	82 (5)	139–141 (137–139)
4	 2d	 4d	63 (6)	168–169	8	 2h	 4h	78 (5)	89–93

[a] Cyanamide (1.0 eq.), benzyl alcohol (2.0 eq.), $FeCl_3$ (30 mol%), DCE (10 mL) as solvent, reflux. [b] Isolated yield.



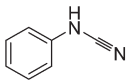
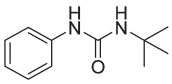
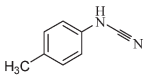
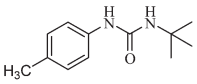
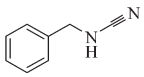
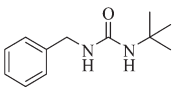
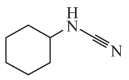
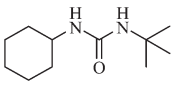
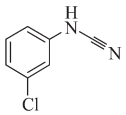
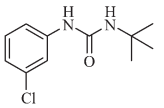
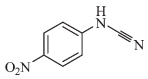
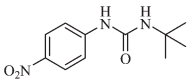
Scheme 2 Synthesis of *N*,*N*′-disubstituted ureas employing *t*-butyl alcohol.

The structures of all the products were confirmed through ^1H and ^{13}C NMR analyses.

In a typical example, in the ^1H NMR spectrum of **2i** a signal appears at δ 4.66 (*NH*CN) and ^{13}C spectrum exhibited a signal at δ 116.7 (NH–*C*≡N). Whereas the ^1H NMR spectrum of **4j** (as a typical example) revealed two signals at δ 5.64 and 6.02 (–N*H*–CO–N*H*–) and ^{13}C spectrum of **4j** showed peak at δ 156.4 (–NH–*C*O–NH–). The disappearance of a peak at δ 116.7 (–NH–*C*≡N) as in the ^{13}C spectrum of **2i** and appearance of a new peak at δ 156.4 corresponding to the carbonyl carbon of urea was observed in the ^{13}C spectrum of **4j**. From the ^1H NMR analyses of both the reactant **2i** and product **4j** it was inferred that, during the transformation there is an apparent downward shift of the –NH proton signal, where NH proton signal in **2i** shifts from δ 4.66 to δ 6.02 in **4j**. Not much significant shift was observed for the benzylic protons, but appearance of a new signal at δ 5.64 corresponding to another –NH proton of urea was observed. Thus NMR analyses of **2i** and **4j** indicated an efficient transformation of cyanamide to corresponding urea in one step.

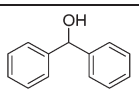
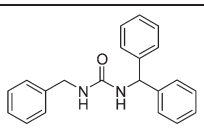
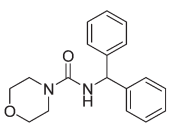
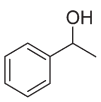
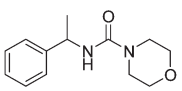
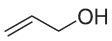
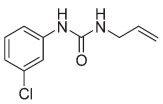
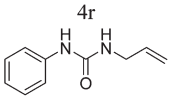
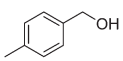
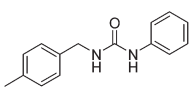
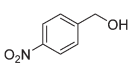
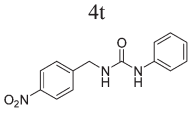
The *t*-butyl ureas (**4i–n**) synthesized through this route could have considerable application as they serve as safe and nonhazardous forms of isocyanate. In the presence of an amine under thermal conditions, *t*-butyl urea dissociates into the corresponding isocyanate and furnishes the desired urea as reported by Shudo.[30] Also, trisubstituted ureas were also accessed by the reaction of cyanamide derived from secondary amines with the benzyl alcohol under the optimized Ritter conditions (**4e–h**). The substituent with electron donating groups enhanced the reactivity both towards the cyanamide formation as well as the corresponding urea preparation (**4b**, **4c**, **4k**, **4l**) compared to their withdrawing counterparts. Substituents with electron withdrawing groups lowered the reactivity of cyanamide to some extent resulting in comparatively lower yields of urea (**4f**, **4d**). The substituted benzyl alcohols (**3f**, **3g**) afford corresponding ureas (**4t**, **4u**) in quantitative yield, despite the nature of the substituent (electron donating or withdrawing). Also, it is worthy to note that the bulkier and sterically hindered alcohols *viz.* *t*-butyl alcohol (**3b**), diphenylmethanol (**3c**) and 1-phenylethanol (**3d**) which can form resonance stabilized carbenium ions, afford desired ureas in good yields (**4i–n**, **4o–q**). The protocol can be applied efficiently to the substrates possessing other functional moieties (**4c**, **4d**, **4f**). However **4d** and **4n** were obtained in lesser yield due to the steric constraint and the electron withdrawing ability of the substituents respectively. In addition, allyl alcohol (**3e**) which forms stable allylic cations stabilized by π electrons of the olefinic double bond was employed and the reaction worked well in furnishing the corresponding allyl ureas (**4r**, **4s**) in excellent yields, which were the interesting class of molecules in polymer science.[31] The notable advantages of this method are the operational simplicity, direct use of cheap and readily available alcohols as precursor elements and inexpensive, nontoxic $FeCl_3$ as catalyst which renders the method an important alternative to existing methods.

Table 3 List of *t*-butyl substituted ureas synthesized through *t*-butyl alcohol

Sl. no.	Cyanamide (2)	Urea (4)[a]	Yield[b] (%), Reactin time (h)	M.P. (°C), Obsd (Lit.)	Sl. no.	Cyanamide (2)	Urea (4)[a]	Yield[b] (%), Rean. time (h)	M.P. (°C), Obsd (Lit.)
9	 2a	 4i	85 (6)	172–174 (171–172)	12	 2j	 4l	83 (6)	185–186 (184–186)
10	 2i	 4j	91(6)	111–114 (109–111)	13	 2k	 4m	87 (7)	224–226 (223–224)
11	 2b	 4k	81(5.5)	175–177	14	 2l	 4n	77 (6)	143–145 (142–143)

[a] Cyanamide (1.30 eq.), *tert*-butyl alcohol (2.0 eq.), $FeCl_3$ (mol%), AcOH (0.5 eq.), DCE (10 mL) as solvent, reflux. [b] Isolated yield.

Table 4 List of *N*,*N*′-di and trisubstituted ureas employing other alcohols

Entry	Alcohol (3)	Urea (4)[a]	Yield[b] (%), Reaction time (h)	M.P. (°C), Obsd (Lit.)
15	 3c	 4o	83 (5)	241–244
16		 4p	81 (5)	181–182 (180)
17	 3d	 4q	80 (6)	84–86 (83–84)
18	 3e	 4r	68 (7)	214–216
19		 4s	73 (7)	191–193
20	 3f	 4t	83 (7)	186–188
21	 3g	 4u	81 (7)	196–198

[a] Cyanamide (1.0 eq.), alcohol (2.0 eq.), $FeCl_3$ (30 mol%), DCE (10 mL) as solvent, reflux. [b] Isolated yield.

Conclusions

In summary, herein we describe an application of the classical Ritter's reaction for the synthesis of unsymmetrical di and trisubstituted ureas catalysed by a safe and eco-friendly reagent system, $FeCl_3$. This protocol is of significant interest in view of the easy availability of precursors, mild reaction conditions employed and interestingly its applicability for the alkylation of alcohols capable of forming stable carbocationic intermediates. Also, the present protocol would provide an excellent alternative due to the environmentally benign system and atom efficiency.

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