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ORIGINAL ARTICLE

An efficient and greener protocol towards synthesis of unsymmetrical *N*,*N*′-biphenyl urea

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Abstract A simple and efficient route for the synthesis of Unsymmetrical *N*,*N*′-diphenyl urea have been developed in aqueous medium under base and catalyst free condition from corresponding substituted isocyanate and amines. The remarkable key feature of the reaction includes the use of water as an inexpensive and environmentally benign reaction medium, absence of base and any additional catalyst, and easy isolation of the product.

1. Introduction

Recent focus on urea stems from its wide range of application in petrochemicals, agrochemicals, and pharmaceuticals and it is also used as dyes for cellulose fibres, (Sartori, 2000) antioxidants in gasoline or as plant growth regulators, pesticides and herbicides. The unsymmetrical urea functional group is also encountered in several biologically active synthetic targets. In particular, potent urea containing HIV-1 protease inhibitors (Cassar, 1990) and p38 kinase inhibitors have recently been disclosed (Lam et al., 1994).

Substituted ureas are very important class of compounds that display a wide range of interesting applications (Li et al., 2006). They have extensively been used as agrochemicals (Hegarty and Drennan, 1995), pharmaceuticals (Greene and Wuts, 1985), intermediates in organic synthesis (Han et al., 1998), for the protection of amino groups (Regan et al., 2002) and as linkers in combinatorial chemistry (Mensal and Gutschow, 2005). These require their preparation by a convenient and safe methodology. Traditionally, their synthesis involves a reaction of amines with phosgene (Smith and March, 2001), and its derivatives (Guichard et al., 1999), carbonyl-imidazoles (Batey et al., 1998), or carbon monoxide (Mccusker et al., 2000) using various kinds of metal and non-metal catalysts.

Despite the growing number of synthetic methodologies, urea is more commonly synthesised by the reaction of an amine

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with phosgene or carbamates. Use of phosgene or phosgene surrogates is still regarded as the traditional method for the formation of urea, at least in the industry. This approach is particularly efficient for symmetrical ureas. In the case of unsymmetrical ureas, the synthetic efficiency is limited by the formation of symmetrical urea side products. In the last few years, toxic and unstable reagents, such as phosgene and isolated isocyanides have been increasingly substituted for cleaner and inherently safer alternatives (Chauhan et al., 2004). These include the use of carbonates or carbonyl imidazole or taking advantage of the reactivity of carbonates' with amines to produce urea.

Unfortunately, production and use of phosgene open many worrying toxicological and environmental problems, such as the use and storage of large amounts of chlorine, production of excess aqueous waste contaminated by chlorine and chlorine bi-products, high environmental risk in storage and transportation of phosgene, use of phosgene characterised by high toxicity and volatility. Nevertheless, about 2 million tons per year of phosgene are produced and utilised worldwide (Frezza et al., 2006). Under the new environmental legalisation of the developed countries, industrial and academic research groups have performed methodologies for preparation of urea based on the use of reagents that are less toxic and less hazardous than phosgene (Mccusker et al., 2000).

Method for preparing 1,3-disubstituted urea through catalytic process by reacting a cyclic carbonic acid ester with an amine were disclosed (US Patent. 5902899, 1999). This method is too expensive to use on a large scale. The transformation of amines to disubstituted urea through catalytic carbonylation provides an alternative environmental benign method and has been investigated over many years using various kinds of metallic catalysts (Mulla et al., 1997). However, these methods failed due to the problems of regenerating the catalysts from the products. Moreover, their formation using CO_2 employed harsh reaction conditions, such as long reaction times, use of expensive strongly basic reagents, tedious work-up, and low yields (Tai et al., 2002). Consequently, there is a continued interest in developing new and convenient methods for the synthesis of substituted urea using mild reaction conditions.

2. Experimental

2.1. Reagents and analysis

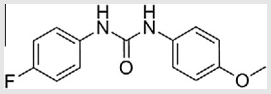
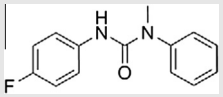
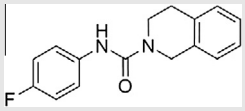
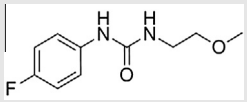
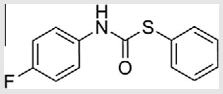
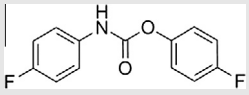
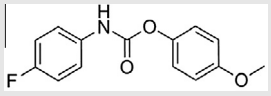
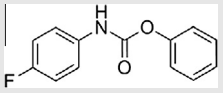
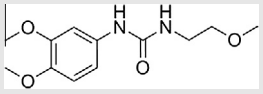
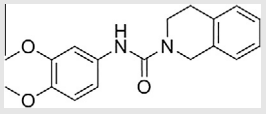
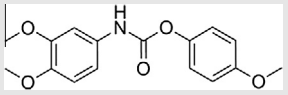
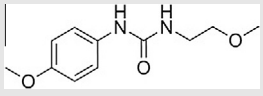
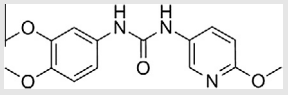
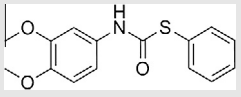
All Reagents were commercial purchased from Aldrich and used without further purification. Commercial reagents were used as received. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm precoated Merck Silica Gel 60 F_{254}, visualising with ultraviolet light or Ninhydrine. ^{1}H NMR spectra were recorded on Bruker DPX-400 with standard pulse sequences, operating at 300 MHz Chemical shifts were in parts per million (ppm) downfield from Tetramethylsilane (TMS), which was used as an internal standard. HPLC-MS analyses were performed with an Agilent Technologies 1100 series consisted of quaternary pump with degasser, auto sampler, column oven and DAD detector.

2.2. General procedure

General procedure: Amine (10 mmol) was dissolved in water and the mixture cooled to 5 °C. After 5 min isocyanate (10 mmol) was slowly added in the above reaction mixture in such way that the temperature of reaction mixture doesn't increase above 5 °C. As the reaction proceeds solid falls out. RM was stirred for 30 min at 5 °C & reaction was monitor by TLC. After completion of the reaction the solid was filtered out & the residue was washed with water. The solid was collected to report yield & analysis of the respective urea. The product was confirmed by melting points and spectral analysis, such as MS, NMR.

Spectral data: (Table 1, entry 1) 1H NMR (300 MHz, DMSO-d_6): δ 8.60 (s, 1H), δ 8.45 (s, 1H), δ 7.45 (dd, J = 9.1, 4.9 Hz, 2H), δ 7.35 (d, J = 9.1 Hz, 2H), δ 7.10 (t, J = 8.9 Hz, 2H), δ 6.87 (d, J = 8.7 Hz, 2H), δ 3.71 (s, 3H); ESI (m/z) Calc. for $C_{14}H_{13}FN_2O_2$: 260.26, Found: 261.11 [M + H]. (Table 1, entry 2) 1H NMR (300 MHz, DMSO-d_6): δ 8.21 (s, 1H), δ 7.38–7.46 (m, 4H), δ 7.30–7.35 (m, 2H), δ 7.21–7.28 (m, 1H), δ 7.02–7.10 (m, 2H), δ 3.26 (s, 3H); ESI (m/z) Calc. for $C_{14}H_{13}FN_2O$: 224.12, Found: 225.21 [M + H]. (Table 1, entry 3) 1H NMR (300 MHz, DMSO-d_6): δ 8.61 (s, 1H), δ 7.45–7.55 (m, 2H), δ 7.19 (s, 4H), δ 7.08 (t, 2H), δ 4.63 (s, 2H), δ 3.69 (t, J = 5.9 Hz, 2H), δ 2.85 (t, J = 6.0 Hz, 2H); ESI (m/z) Calc. for $C_{16}H_{15}FN_2O$: 270.12, Found: 271.11 [M + H]. (Table 1, entry 4) 1H NMR (300 MHz, DMSO-d_6): δ 8.54 (s, 1H), δ 7.37 (dd, J = 9.3, 5.1 Hz, 2H), δ 7.05 (t, J = 9.1 Hz, 2H), δ 6.16 (t, J = 5.5 Hz, 1H), δ 3.32–3.40 (m, 5H), δ 3.21–3.25 (m, 2H); ESI (m/z) Calc. for $C_{10}H_{13}FN_2O_2$: 212.22, Found: 213.23 [M + H]. (Table 1, entry 5) 1H NMR (300 MHz, DMSO-d_6): δ 10.57 (s, 1H), δ 7.48–7.56 (m, 4H), δ 7.44–7.48 (m, 3H), δ 7.12–7.19 (m, 2H); ESI (m/z) Calc. for $C_{13}H_{10}FNOS$: 247.29, Found: 248.29 [M + H]. (Table 1, entry 6) 1H NMR (300 MHz, DMSO-d_6): δ 10.29 (br s, 1H), δ 7.51 (dd, J = 9.1, 4.9 Hz, 2H), δ 7.24–7.29 (m, 4H), δ 7.18 (t, J = 8.9 Hz, 2H); ESI (m/z) Calc. for $C_{13}H_9F2NO2$: 249.21, Found: 250.01 [M + H]. (Table 1, entry 7) 1H NMR (300 MHz, DMSO-d_6): δ 10.20 (br s, 1H), δ 7.51 (dd, J = 9.1, 4.9 Hz, 2H), δ 7.09–7.22 (m, 4H), δ 6.95 (d, J = 9.1 Hz, 2H), δ 3.76 (s, 3H); ESI (m/z) Calc. for $C_{14}H_{12}FNO_3$ 261.25, Found: 262.15 [M + H]. (Table 1, entry 8) 1H NMR (300 MHz, DMSO-d_6): δ 10.27 (br s, 1H), δ 7.52 (dd, J = 9.1, 4.9 Hz, 2H), δ 7.39–7.47 (m, 2H), δ 7.13–7.30 (m, 5H); ESI (m/z) Calc. for $C_{13}H_{10}FNO_2$: 231.22, Found: 232.54 [M + H]. (Table 1, entry 9) 1H NMR (300 MHz, DMSO-d_6): δ 8.34 (s, 1H), δ 7.15 (d, J = 2.3 Hz, 1H), δ 6.76–6.83 (m, 2H), δ 6.05–6.11 (m, 1H), δ 3.70 (s, 4H), δ 3.68 (s, 3H), δ 3.36 (s, 2H), δ 3.27 (s, 3H), δ 3.19–3.26 (m, 2H); ESI (m/z) Calc. for $C_{12}H_{18}N_2O_4$: 254.17, Found: 255.15 [M + H]. (Table 1, entry 10) ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.40 (s, 1H), δ 7.18 (s, 5H), δ 7.00 (d, J = 8.7 Hz, 1H), δ 6.83 (d, J = 8.7 Hz, 1H), δ 4.62 (s, 2H), δ 3.70 (d, J = 4.2 Hz, 8H), δ 2.84 (t, J = 5.9 Hz, 2H); ESI (m/z) Calc. for $C_{18}H_{20}N_2O_3$: 312.26, Found: 313.32 [M + H]. (Table 1, entry 12) ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30 (s, 1H), δ 7.27 (d, J = 9.1 Hz, 2H), δ 6.80 (d, J = 9.1 Hz, 2H), δ 6.07 (t, J = 5.5 Hz, 1H), δ 3.69 (s,3H), δ 3.35–3.41 (m, 4H), δ 3.27 (s, 3H); ESI (m/z) Calc. for $C_{11}H_{16}N_2O_3$: 224.12, Found: 225.21 [M + H]. Table 1, entry 13) 1H NMR (DMSO-d_6, 300 MHz): δ 8.53 (s, 1H), δ 8.48 (s, 1H), δ 8.17 (d, J = 2.3 Hz, 1H), δ 7.82 (d, J = 8.9, 2.8 Hz, 1H), δ 7.18 (s, 1H), δ 6.86 (s, 2H), δ 6.77 (d,J = 8.7 Hz, 1H), δ 3.81 (s, 3H), δ 3.73 (s, 3H), δ 3.70 (s, 3H); ESI (m/z) Calc. for $C_{15}H_{17}N_3O_4$: 303.12, Found: 304.26 [M + H]. (Table 1, entry 14) 1H NMR (300 MHz,

Table 1 Synthesis of *N,N′*-biphenyl urea.

Sr.No.	Product	Time (h)	Yield[a] (%)	Mp (°C)
1		0.5	85	233–237
2		1	80	120–125
3		0.5	91	145–150
4		2	82	135–140
5		3	73	–
6		2	77	155–157
7		2	80	157–160
8		2	75	125–127
9		1.5	80	77–80
10		0.5	87	132–134
11		1	75	140–142
12		1.5	80	130–132
13		0.5	94	196–198
14		3	72	120

[a] Isolated yields.

DMSO-d_6): δ 10.35 (s, 1H), δ 7.50–7.55 (m, 2H), δ 7.42–7.47 (m, 3H), δ 7.21 (d, J = 2.1 Hz, 1H), δ 6.95–7.01 (m, 1H), δ 6.86–6.91 (m, 1H), δ 3.71 (d,J = 3.0 Hz, 6H) ESI (m/z) Calc. for $C_{15}H_{15}NO_3S$: 289.35, Found: 290.21 [M + H].

3. Results and discussion

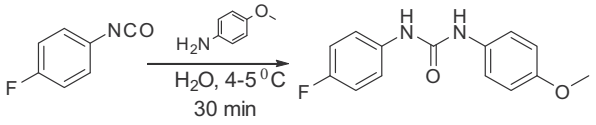
Most of the synthetic approaches to produce urea utilise phosgene or its tamed analogues. Commercially available reagents, such as benzyl isocyanate & phenyl isocyanate also effectively convert into the corresponding disubstituted urea under dry reaction condition. Reaction of phenyl isocyanate in 1,4-dioxane/water or pyridine/water was unable to gives the desired 1,3-diphenylurea in required yield (Liu et al., 2001). Reaction was very slow and takes about 12–16 h to complete. Reagents like isocyanate might not withstand in aqueous condition or react efficiently with complex starting materials. According to our knowledge there was no method for synthesis of urea in water from isocyanate and amine. We have, therefore, sought to develop a methodology which should be Simple, scalable & eco friendly to produced disubstituted urea, Use of the reagent that is electrophonic enough and effectively react with amines of various structures, yet reasonably stable in aqueous environments.

Reaction of 1-fluoro-4-isocyanatobenzene with anisole in aq. Medium gives desired urea in very low yield (10%) and it takes 10–15 h to complete the reaction. This could be due to instability of isocyanate in water. When we repeated same reaction in water at 4–5 °C, excellent yield of the desired urea was observed in 30 min. From the above observation we conclude that reagent like isocyanate may be stable in aq medium at lower temperatures. Although this was our observation in this particular case, however, we do not have any proof for the stability of such reagent in water at lower temperatures.

To test the feasibility and practical applicability, a reaction on large scale was conducted in water at 4–5 °C; 85% of conversion was observed after 30 min. The mixture was just filtered out to get pure biphenyl urea. As the yields of the products obtained in ordinary tap water and distilled water were comparable, all reactions were carried out in tap water so that the consumption of energy and efforts needed to prepare distilled water can be avoided (see).

Anisole was dissolved in water (complete or partial) and the mixture was cooled to 5 °C. After 5 min 1 mol equiv of 1-fluoro-4-isocyanatobenzene was slowly added in the above reaction mixture in such way that the temperature of reaction mixture doesn't rise above 10 °C. As the reaction proceeds the solid falls out. RM was stirred for 30 min at 5 °C & the reaction was monitored by TLC. The solid was filtered out & the residue washed with water. the obtained product does not require further purification. The solid was collected to report yield and analysis.

Under optimised reaction condition, the scope of reaction was explored with structurally and electronically diverse amine, thiols, alcohol and isocyanate to get respective urea, thiourea & carbamate.



Scheme 1

Monosubstituted aryl amine such as n methyl phenyl amine treated with 1-fluoro-4-isocyanatobenzene under similar condition gives 80% yield. Also good yield was obtained in case of amine which was partially soluble in aq. medium at lower temperatures. Reaction of *p*-nitro aniline with 1-fluoro-4-isocyanatobenzene failed to give the desired product under similar reaction condition. This may be because of a decrease in nucleophilicity of amine due to the p-nitro group. Then we decided to generalise our methodology for the synthesis of Thiourea & carbamate.

Thiol when treated with 1-fluoro-4-isocyanatobenzene gives the corresponding thiourea. Similarly when phenol was treated with 1-fluoro-4-isocyanatobenzene it gives the corresponding carbamate. We found slightly lower yields of thiourea & carbamate as compared to urea. We also observed low yields when *n*-methyl phenyl amine was treated with 1-fluoro-4-isocyanatobenzene. From the above observation we conclude that low yield was due to a decrease in nucleophilicity of phenol, thiols & monosubstituted aryl amine in aq. medium. Advantage of the above method was that the obtained product doesn't require further purification such as column chromatography or recrystallisation. The above Method is simple, economical, efficient, and high yielding one-pot synthesis of unsymmetrical disubstituted urea.

The product was confirmed by melting points and spectral analysis such as MS, NMR.

4. Conclusion

In this communication, we report a simple, economical, efficient, high yielding one-pot synthesis of unsymmetrical disubstituted urea, from the corresponding isocyanates under aqueous medium. The remarkable key feature of the reaction includes the use of water as an inexpensive and environmentally benign reaction medium, absence of base and any additional catalyst, and easy isolation of the product. We believed that this synthesis protocol offer a more general method for the formation of C–N, C–O & C–S bonds essential to numerous organic syntheses. Various unsymmetrical disubstituted ureas, thiourea derivatives (Table 1) were prepared in high yields and their spectroscopic confirmation was achieved.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arabjc.2011.01.030.

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