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RESEARCH ARTICLE

$ZrOCl_2.8H_2O$: An Efficient Catalyst for the Synthesis of *N,N'*-Disubstituted Ureas from Biuret Under Solvent Free Conditions

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Abstract: A green and facile synthesis of *N,N*'-disubstituted urea from biuret and different amines have been developed using $ZrOCl_2.8H_2O$ as catalyst in the absence of solvent under microwave irradiations. The remarkable features of this protocol are higher yield in shorter reaction time, use of non-toxic and readily available catalyst, clement and environment affable reaction conditions and simple work up procedures.

Keywords: $ZrOCl_2.8H_2O$, Biuret, Amines, Solvent free conditions

Introduction

Urea and its derivatives are versatile organic compounds present in a number of naturally occurring compounds and are associated with a wide range of therapeutic and pharmaceutical applications as HIV-1 protease inhibitors[1], Raf kinase inhibitors[2], peptidomimetics[3], cytokinin analogous[4], anti-melanoma agents[5], inhibitors of Murine receptor A and Murine receptor B[6], antihyperglycaemic agents[7], antagonists of human vanilloid VR 1 receptors[8], anti tuberculosis agents[9], potent inhibitors of influenza virus neuraminidase[10] and diuretics[11]. Several urea derivatives are used as plant growth regulators, herbicides, pesticides, corrosion inhibitors, antioxidant, dyes for cellulose fibers, antidiabetic and tranquillizing drugs[12-14]. A large number of methods are reported for the synthesis of urea derivatives including oxidative[15] and reductive carbonylation[16] of amines, reaction of amines with phosgene and its derivatives[11,17], carbmates[18], isocynates[19], or by reaction of urea or thiourea with amines[20]. Different catalytic systems are also reported for synthesis of urea derivatives such as iodine[21], zinc chloride[22], Cs_2CO_3[23], titanium (IV)isopropoxide and sodium borohydride[24], $CeCl_3.7H_2O$-KI[25], PEG-400[26] and zeolite HSZ-360[14]. The limitations associated with the reported methods are harsh reaction conditions, lower yields, longer reaction times, tedious isolation and purification procedures and use of organic solvents. Organic solvents are highly volatile and carcinogenic in nature and are extremely hazardous to human health and environment. Phosgene, carbamates and isocynates used during phosgenation are expensive and hazardous reagents. CO used during oxidative carbonylation is toxic and difficult to handle.

In recent times, zirconium oxychloride octahydrate ($ZrOCl_2.8H_2O$) is used as a potent Lewis acid catalyst in a variety of organic reactions[27-31] providing excellent yields with marked selectivity. Unlike traditional Lewis acids, $ZrOCl_2.8H_2O$ is non-toxic, moisture stable, easy to handle, readily available oxy salt of zirconium and widely used as a green catalyst. Further, microwave assisted reactions under solvent free conditions has gained considerable attention in synthetic organic chemistry owing to many advantages such as energy efficiency, higher yields, ease of reaction condition and enhanced selectivity. In an efforts towards developing clean and efficient methodology using non-toxic reagent under mild reaction conditions, herein we report an efficient synthesis of *N,N'*-disubstituted ureas by reaction of biuret with differently substituted amines using $ZrOCl_2.8H_2O$ as catalyst in the absence of solvent under microwave irradiations.

Experimental

All chemicals were purchased from Sigma-Aldrich and used without further purification. $ZrOCl_2.8H_2O$ was purchased from Fluka Goldie. Melting points were determined in open capillaries and are uncorrected. The reactions were carried out in a Samsung microwave oven operating between 80-800W, Model No. CE745G. IR spectra were recorded on Perkin-Elmer spectrum BX Series FT-IR spectrophotometer with KBr pellets. ^{1}H NMR was recorded on a 400 MHz spectrometer Bruker Avance Π 400 using Tetramethylsilane (TMS) as internal standard.

General procedure for the synthesis of N,N'-disubstituted urea derivatives

Biuret (0.103 g, 1 mmol), aniline (0.18 mL, 2 mmol) and $ZrOCl_2.8H_2O$ (200 mg) were taken in a 10 mL Pyrex beaker, stirred for a few minutes at room temperature and then exposed to microwave irradiations at 180 W. The progress of reaction was monitored by TLC (CCl_4: Ethyl acetate/4: 1) and the reaction was found to be completed after 8 min. The reaction mixture was diluted with ice cold water and the solid thus separated out was filtered at vacuum; washed with water and recrystallized from ethanol to give *N,N'*- diphenylurea in 80% yield.

Identical procedure was followed for the preparation of other *N,N'*-disubstituted ureas under similar reaction conditions. The products were recognized on the basis of spectroscopic data and melting point comparison with the authentic samples[22,25,32,33].

N,N'-Diphenylurea

IR (KBr, cm^{-1}): 3215 (N-H), 3079 (C-H), 1699 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (br, 2H, NH), 7.45 (d, J=8.8 Hz, 4H), 7.24 (t, 4H), 6.95 (t, 2H).

N,N'-bis(2-Methylphenyl)urea

IR (KBr, cm^{-1}): 3401 (N-H), 3108 (C-H), 1690 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (br, 2H, NH), 7.48-7.37 (m, 2H), 7.31-7.16 (m, 4H), 6.96-6.93 (m, 2H), 2.09 (s, 6H).

N,N'-bis(4-Methylphenyl)urea

IR (KBr, cm^{-1}): 3305 (N-H), 3032 (C-H), 1640 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (br, 2H, NH), 7.34-7.25 (m, 4H), 7.10-6.99 (m, 4H), 2.29 (s, 6H).

N,N'-bis(2-Methoxyphenyl)urea

IR (KBr, cm^{-1}): 3415 (N-H), 3040 (C-H), 1668 (C=0), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (br, 2H, NH), 7.23-7.21 (m, 2H), 7.06-7.02 (m, 2H), 6.74-6.72 (m, 2H), 6.69-6.65 (m, 2H), 3.63 (s, 6H).

N,N'-bis(4-Methoxyphenyl)urea

IR (KBr, cm^{-1}): 3418 (N-H), 3030 (C-H), 1627 (C=0), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (br, 2H, NH), 6.98-6.64 (m, 2H), 6.54-6.44 (m, 4H), 3.36 (s, 6H).

N,N'-bis(2-Nitrophenyl)urea

IR (KBr, cm^{-1}): 3370 (N-H), 3085 (C-H), 1687 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (br, 2H, NH), 7.82 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.4 Hz, 2H), 7.28 (t, 2H), 7.08 (t, 2H).

N,N'-bis(4-Nitrophenyl)urea

IR (KBr, cm^{1}): 3451 (N-H), 3080 (C-H), 1680 (C=0), ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.49 (br, 2H, NH), 8.11-7.64 (m, 4H), 6.70-6.61 (m, 4H).

N,N'-bis(2-Chlorophenyl)urea

IR (KBr, cm^{-1}): 3338 (N-H), 3095 (C-H), 1695 (C=0); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.38 (br, 2H, NH), 7.53-7.37 (m, 4H), 7.07-6.80 (m, 4H).

N,N'-bis(Phenylamino)urea

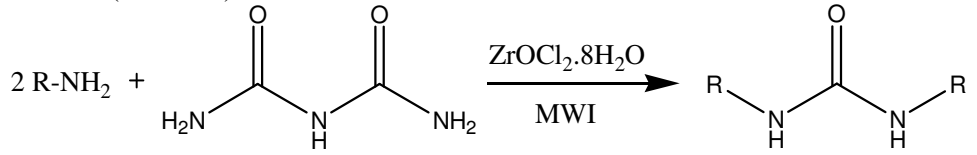
IR (KBr, cm^{-1}): 3398 (N-H), 3060 (C-H), 1689 (C=0); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.14 (br, 2H, NH), 8.19 (d, 2H, NH), 7.97-7.21 (m, 10H).

N,N'-bis(Cyclohexyl)urea

IR (KBr, cm^{-1}): 3401 (N-H), 3110 (C-H), 1695 (C=0), ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.55 (br, 2H, NH), 3.37 (m, 2H), 1.78-1.50 (m, 10H), 1.31-1.18 (m, 10H).

Results and Discussion

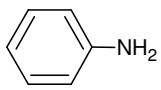
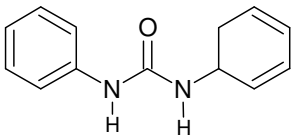
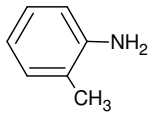
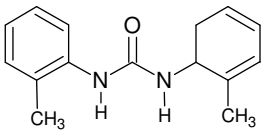
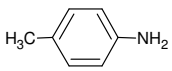
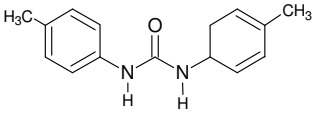
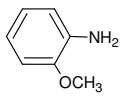
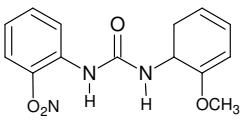
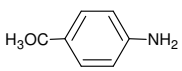
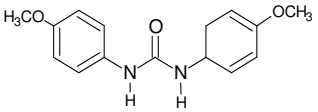
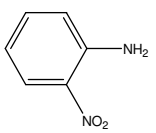
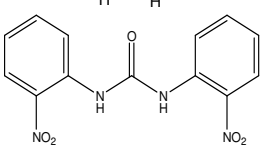
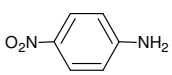
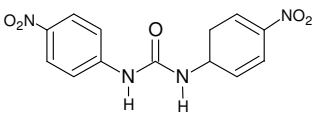
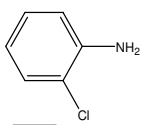
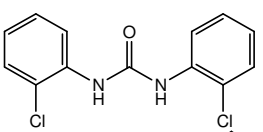
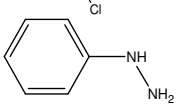
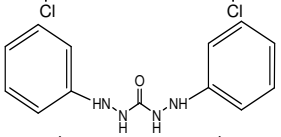
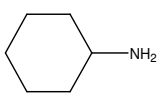
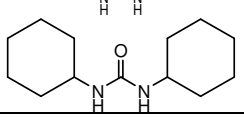
In a typical procedure, biuret and aniline taken in 1:2 molar ratio were subjected to microwave irradiations in the presence of a catalytic amount of $ZrOCl_2.8H_2O$ under solvent free conditions. The progress of reaction was monitored by TLC and the reaction was found to be completed in 8 min. The compound obtained after workup (80%, m.pt. 241 °C) in its IR exhibited a band at 3215 cm^{-1} which was attributed to N-H stretching, 3079 cm^{-1} due to C-H stretching and 1699 cm^{-1} due to C=O stretching. In ^{1}H NMR spectra the compound exhibited a singlet at δ 8.45 due to two NH protons, a doublet at δ 7.45 (J=8.8 Hz) due to four aromatic protons, a triplet at δ 7.24 due to four aromatic protons and a triplet at δ 6.95 due to two aromatic protons. Based on its IR, ^{1}H NMR and melting point comparison with literature value the compound was identified as *N,N'*-diphenylurea. Similar procedure was extended to other amines substituted with electron donating and electron withdrawing substituent for synthesizing various *N,N'*-disubstituted ureas under identical reaction conditions (Scheme 1).



Scheme 1. $ZrOCl_2.8H_2O$ catalyzed synthesis of *N,N'*-disubstituted ureas

Rapid synthesis of *N,N'*-disubstituted ureas in the given reaction conditions, may be pertained due to the mild acidic environment created by $ZrOCl_2.8H_2O$ which makes the carbonyl carbon more susceptible towards the nucleophilic attack of the amine and hence increasing the yield and selectivity (Table 1).

Table 1. Synthesis of *N,N'*-disubstituted ureas from biuret and various amines (1:2) at 180 W in the presence of $ZrOCl_2.8H_2O$

Entry	Substrate	Product	Yield[a] %	Time min	M.P.(Lit.) °C
1a			80	08	241(242)[22]
1b			86	06	233(235)[33]
1c			88	06	267(269)[22]
1d			80	08	184(185)[25]
1e			85	10	239(240)[22]
1f			66	12	224(226-28)[32]
1g			76	10	303(305-06)[22]
1h			78	10	224(225-26)[25]
1i			84	08	172(171-73)[22]
1j			86	07	203(205-06)[22]

[a]*Yields are of pure product isolated*

Conclusion

We have developed an efficient method for the synthesis of *N,N'*-disubstituted ureas as it avoids the use of hazardous organic solvent at any stage of the reaction. The anticipated ureas were obtained under clean and milder conditions with a simple work-up procedure.

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