Microwave-Assisted Efficient Synthesis of Dialkylated Ureas from Ureas

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Abstract. Microwave irradiation provided an effective tool for rapid, clean, and high-yielding transformations of organic reactions. Despite these advances, the N-alkylation of amines with alcohols under microwave irradiation remains less unexplored. We demonstrated a general and efficient method for the synthesis of dialkylated ureas from ureas under microwave irradiation is described. Reactions of ureas with a series of alcohols, such as benzyl alcohol, benzylic alcohols bearing a electron-donating group or a electron-withdrawing group, afforded the desired dialkylated ureas with good yields at a short time. Experimental results exhibited obvious advantages of microwave irradiation.

Introduction

The N-alkylation of amines is one of the most important C-N bond-forming reactions in the field of organic synthesis.[1] Traditionally, the N-alkylation of amines was performed with alkyl halides in the presence stoichiometric bases. Recently, much attention has been paid to the N-alkylation of amines with alcohols as environmentally benign alkylating agents instead of alkyl halides for the preparation of N-alkylated amines based on “hydrogen autotransfer” process, using iridium, ruthenium, or other transition metal catalysts.[2-8] In this process, alcohols are first dehydrogenated to form aldehydes with the generation of metal hydride species, then condensation between the resulting aldehydes and ketones occurs to afford imines, which undergo transfer hydrogenation to give the final N-alkylated amines. This method is apparently attractive due to the formation of water as the only side product (Scheme 1).

Scheme 1 Transition metal-catalyzed N-alkylation of amines with alcohols

In recent years, microwave irradiation has been widely employed as an effective reaction acceleration protocol, resulting in rapid, clean, and high-yielding transformations.[9] Despite these advances, the N-alkylation of amines with alcohols under microwave irradiation remains less unexplored.[10] We have reported iridium-catalyzed synthesis of dialkylated ureas from ureas and alcohols.[11-12] The dialkylated ureas are important class of biologically active compounds. However, the reaction required long reaction time (12 h).[13] Therefore, herein we wish to demonstrate that microwave irradiation significantly accelerated the process of the reaction.

Results and Discussion

Our initial experiment focused on N-alkylation of urea **1** with benzyl alcohol **2a**. The reaction of **1** was carried out in the presence of $[\text{Cp}^*\text{IrCl}_2]_2$ (0.4 mol%)/KOH (1 equiv.) at 110 °C under microwave irradiation. To our surprise, the dialkylated product **3aa** could be obtained with 82% yield after reaction proceed for 2h (Scheme 2).

Scheme 2 N-alkylation of **1** with benzyl alcohol **2a** under microwave irradiation

To explore the scope of reaction, the N-alkylation of **1** with various alcohols **2** was investigated under established conditions (Scheme 2) and these results were shown in Table 1. Reactions with benzylic alcohols bearing an electron-donating groups, such as 4-methyl **2b**, 4-isopropyl **2c** and 4-methoxyl **2d**, afforded the desired products **3b-3d** with 68-72% yields (Table 1, entries 1-3). Similarly, benzylic alcohols bearing one or two halogen atoms, such as 4-chloro **2e**, 2,4-dichloro **2f** and 4-bromo **2g**, were also proven to be suitable substrates, and the desired products **3e-3g** were obtained with 77-80% yields (Table 1, entries 4-6). The N-alkylation with benzylic alcohols bearing an electron-withdrawing trifluoromethyl **2h** gave the corresponding products **3h** with 73% yield (Table 1, entry 7).

Conclusions

We have described a general and efficient method for the synthesis of dialkylated ureas from ureas under microwave irradiation. A series of products were obtained with high yields at a short time. Experimental results exhibited obvious advantages of microwave irradiation.

Experimental Section

General Experimental Details. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 500 MHz using a Bruker Avance 500 spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane or ppm relative to the center of the singlet at 7.26 ppm for CDCl_3 and 2.50 ppm for DMSO-d_6 . Coupling constants J values are reported in Hertz (Hz), and the splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 125 MHz using a Bruker Avance 500 spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for CDCl_3 and 39.5 ppm for DMSO-d_6 . ^{13}C NMR spectra were routinely run with broadband decoupling.

Microwave-Assisted synthesis of dialkylated ureas from ureas: Urea (1 mmol), alcohol (2 mmol), $[\text{Cp}^*\text{IrCl}_2]_2$ (1 mol%), KOH (1.0 mmol, 1.0 equiv.), 1 mL *tert*-amyl alcohol were added to a microwave vial containing a stirrer bar. The vial was then sealed before purging with nitrogen gas for 5 min. The mixture was then heated at 110 °C for 2 h under microwave irradiation (300 W, sealed reaction vessel), and was cooled to ambient temperature, concentrated in *vacuo* and purified by flash column chromatography with hexanes/ethyl acetate to afford the corresponding product.

1,3-dibenzylurea (3a). ^1H NMR (500 MHz, CDCl_3) δ 7.30–7.28 (m, 4 H, ArH), 7.26–7.23 (m, 6 H, ArH), 4.89 (t, J = 5.0 Hz, 2H, NH), 4.33 (d, J = 5.7 Hz, 4 H, $2\times\text{CH}_2$); ^{13}C NMR (125 MHz, CDCl_3) δ

Table 2 N-Alkylation of **1a** with various alcohols **2** under microwave irradiation^[a]

$ \begin{array}{c} \text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}_2 \\ \mathbf{1} \end{array} + \begin{array}{c} \text{X}-\text{C}_6\text{H}_4-\text{CH}_2\text{OH} \\ \mathbf{2} \end{array} \xrightarrow[\text{t-amyl alcohol, 110 }^\circ\text{C, 2 h}]{[\text{Cp}^*\text{IrCl}_2]_2 \text{ (0.4 mol\%)} \\ \text{KOH (0.4 equiv.)}} \begin{array}{c} \text{X}-\text{C}_6\text{H}_4-\text{CH}_2\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-\text{C}_6\text{H}_4-\text{X} \\ \mathbf{3} \end{array} $			
Entry	Alcohol	Product	Yield [%] ^[b]
1	2b	3b	71
2	2c	3c	68
3	2d	3d	78
4	2e	3e	80
5	2f	3f	79
6	2g	3g	77
7	2h	3h	73

[a] Reaction conditions: **1a** (1 mmol), **2** (2 mmol), [Cp*IrCl₂]₂ (0.4 mol%), KOH (0.4 equiv.), *t*-amyl alcohol (1 mL), T=110 °C, t = 2 h. [b] Isolated yield.

158.4, 139.2, 128.5, 127.3, 127.2, 44.4.

1,3-bis(4-methylbenzyl)urea (3b). ¹H NMR (500 MHz, DMSO-d₆) δ 7.11 (q, *J* = 6.95 Hz, 8H, ArH), 6.42 (t, *J* = 5.9 Hz, 2H, NH), 4.16 (d, *J* = 5.9 Hz, 4H, CH₂), 2.26 (s, 6H, CH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ 158.43, 138.21, 135.63, 129.28, 127.63, 43.01, 21.15.

1,3-bis(4-isopropylbenzyl)urea (3c). ^1H NMR (500 MHz, DMSO- d_6) δ 7.16 (s, 8H, ArH), 6.33 (t, J = 5.2 Hz, 2H, NH), 4.17 (d, J = 5.2 Hz, 4H, CH_2), 2.85 (quint, J = 6.45 Hz, 2H, CH), 1.18 (d, J = 6.6 Hz, 12H, CH_3); ^{13}C NMR (125 MHz, DMSO- d_6) δ 158.29, 146.96, 138.48, 127.35, 126.33, 43.04, 33.36, 24.21.

1,3-bis(4-methoxybenzyl)urea (3d). ^1H NMR (500 MHz, DMSO- d_6) δ 7.17 (s, 4 H, ArH), 6.87 (s, 4H, ArH), 6.29 (s, 2H, NH), 4.14 (s, 4H, CH_2), 3.72 ppm (s, 6H, OCH_3); ^{13}C NMR (125 MHz, DMSO- d_6) δ 158.0, 157.9, 132.7, 128.3, 113.6, 55.0, 42.4.

1,3-bis(4-chlorobenzyl)urea (3e). ^1H NMR (500 MHz, DMSO- d_6) δ 7.36 (d, J = 8.00 Hz, 4H, ArH), 7.26 (d, J = 8.35 Hz, 4H, ArH), 6.68 (t, J = 5.95 Hz, 2H, NH), 4.20 (d, J = 6.1 Hz, 4H, CH_2); ^{13}C NMR (125 MHz, DMSO- d_6) δ 158.43, 140.33, 131.16, 129.28, 128.38, 42.54.

1,3-bis(2,4-dichlorobenzyl)urea (3f). ^1H NMR (500 MHz, DMSO- d_6) δ 7.58 (s, 2H, ArH), 7.43 (d, J = 7.2 Hz, 2H, ArH), 7.34 (d, J = 7.6 Hz, 2H, ArH), 6.70 (t, J = 5.6 Hz, 2H, NH), 4.26 (d, J = 4.2 Hz, 4H, CH_2); ^{13}C NMR (125 MHz, DMSO- d_6) δ 158.00, 137.27, 132.97, 132.18, 130.19, 128.71, 127.52, 40.78.

1,3-bis(4-bromobenzyl)urea (3g). ^1H NMR (500 MHz, DMSO- d_6) δ 7.49 (d, J = 8.7 Hz, 4H, ArH), 7.20 (d, J = 8.7 Hz, 4H, ArH), 6.66 (t, J = 5.90 Hz, 2H, NH), 4.18 (d, J = 6.25 Hz, 4H, CH_2); ^{13}C NMR (125 MHz, DMSO- d_6) δ 158.55, 140.93, 131.67, 130.09, 120.15, 42.68.

1,3-bis(4-(trifluoromethyl)benzyl)urea (3h). ^1H NMR (500 MHz, DMSO- d_6) δ 7.68 (d, J = 7.3 Hz, 4H, ArH), 7.46 (d, J = 7.2 Hz, 4H, ArH), 6.68 (t, J = 5.4 Hz, 2H, NH), 4.31 (d, J = 4.8 Hz, 4H, CH_2); ^{13}C NMR (125 MHz, DMSO- d_6) δ 158.0, 145.9, 127.5, 127.2 (q, $J_{\text{C-F}}$ = 31.6 Hz), 125.0 (d, $J_{\text{C-F}}$ = 3.5 Hz), 124.3 (q, $J_{\text{C-F}}$ = 270.0 Hz), 42.6.

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