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Super fast cobalt carbonyl-mediated synthesis of ureas

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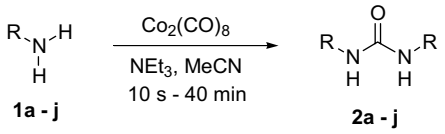
Abstract—Fast cobalt carbonyl-mediated generation of ureas from primary amines was performed using high-density microwave irradiation. This enhanced method permitted the preparation of symmetrical ureas in good yields and unsymmetrical ureas in moderate yields. The reaction times varied between 10 s and 40 min. The proposed mechanism for the reaction includes in situ generation of an intermediate isocyanate that subsequently traps the free amine, producing the urea product.

1. Introduction

Ureas are of fundamental importance in both pharmaceutical and agricultural applications but demand sensitive and aggressive reagents when manufactured. The classical synthetic methods are based on the use of phosgene,[1] isocyanates,[2] or carbonyldiimidazole.[3] Alternatively, protocols for the generation of urea structures by metal-catalyzed oxidative carbonylation under high-pressure CO-gas have been identified.[4,5] Examples of urea syntheses in domestic microwave oven were also recently reported.[6,7]

The development of high-speed synthesis continues to be a key objective within the explorative pharmaceutical industry.[8] In laboratories of today, the increasing use of automation, together with the invention of dedicated equipment for high-throughput purification have greatly accelerated compound production.[9] Controlled microwave irradiation has proved to be an additional powerful technique both for enhancing preparative chemistry and for speeding up the 'hypothesis-iteration' process in the optimization of novel chemistry.[10,11] The synthetic expedience of this heating method is of special importance for reactions requiring a high temperature and harsh conditions. We have applied this form of super heating previously in our attempts to discover not only fast reactions, but super fast organic reactions.[12] Thus, our group recently reported highly stereo-



Scheme 1.

selective transformations and new functional group interconversions after only 10–15 s of single-mode microwave heating.[13,14] In this short communication, we wish to present the successful enhancement of a hitherto little developed dicobalt octacarbonyl-mediated

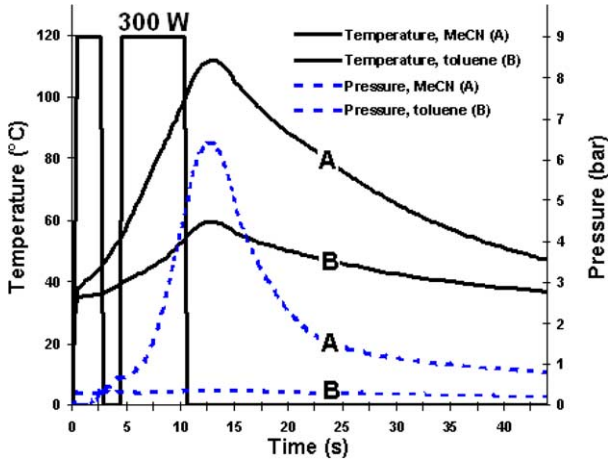


Figure 1. Temperature, power, and pressure profiles from 10 s of microwave heating (Table 1, entry 1). Note that the microwave power is divided into two separate pulses separated by 2 s.[13]

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protocol for direct and CO-free[15] high-speed preparation of ureas from various amines.

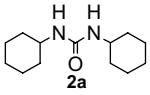
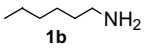
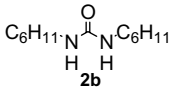
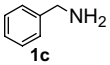
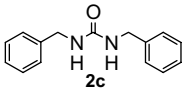
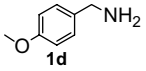
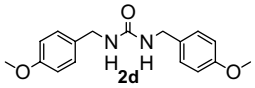
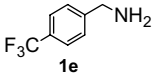
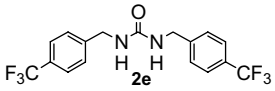
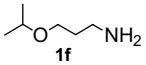
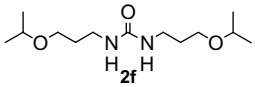
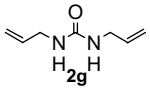
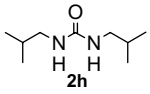
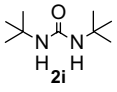
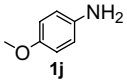
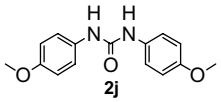
1.1. Symmetrical ureas

Initial experiments were carried out using $Co_2(CO)_8$ and several primary amines **1** to assess appropriate conditions for the microwave-assisted amine to urea **2** transformation depicted in Scheme 1. Importantly, the reactions were carried out in sealed microwave-transparent vessels under air without an external CO-source.[15] Several bases,[16] additives,[17] and solvents of different metal-coordinating ability were evaluated. The results obtained during these studies provided the selected reaction conditions. The choice of acetonitrile as solvent was not self-evident, especially compared to the preparative results with non-polar toluene.

Acetonitrile is a frequently used solvent for reactions performed under microwave irradiation because of its relatively high ability to absorb microwave energy.[10]

In contrast, toluene has a lower dissipation factor and therefore a slower heating profile (Fig. 1). To compare

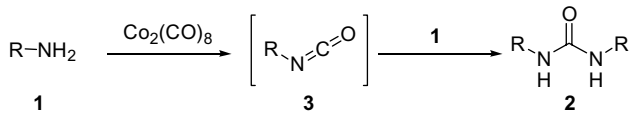
Table 1. Rapid microwave-heated generation of symmetrical ureas from primary amines[a]

Entry	Amine	Time (s)	Temp (°C)	Product	Yield[b] (%)
1	 **1a**	10	Variable	 **2a**	84
		10	Variable		62[c]
		10	Variable		61[d]
		10	Variable		84[e]
		5 h	Rt		75
2	 **1b**	10	Variable	 **2b**	83
		5 h	Rt		81
3	 **1c**	13	Variable	 **2c**	74
		600	130[g]		75[f]
4	 **1d**	10	Variable	 **2d**	66
5	 **1e**	10	Variable	 **2e**	68
6	 **1f**	10	Variable	 **2f**	86
			Variable		61[e]
7	 **1g**	10	Variable	 **2g**	10
8	 **1h**	1200	120[g]	 **2h**	61
9	 **1i**	1200	120[g]	 **2i**	38
10	 **1j**	2400	150[g]	 **2j**	46[f]

[a] Employing 1.0 equiv amine, 0.66 equiv $Co_2(CO)_8$, and 2.0 equiv triethylamine in 2.5 mL acetonitrile.
[b] Isolated yield based on **1** (>95% purity of **2** by GC–MS). Variable temp (T_{max} = 120 °C, see Fig. 1).
[c] DMSO as solvent. Variable temp (T_{max} = 105 °C).
[d] THF as solvent. Variable temp (T_{max} = 105 °C).
[e] Toluene as solvent. Variable temp (T_{max} = 60 °C, see Fig. 1).
[f] 1.0 equiv of propylene carbonate added.
[g] Constant temp.

the two solvents, a set of test reactions was performed using amines **1a** and **f** (Table 1). It is interesting to note the identical yield after a 10 s reaction time (entry 1) with the outcome in entry 6. Thus, to identify a general protocol, acetonitrile was chosen as the standard solvent. All entries in Table 1 were optimized toward reaction rate and reaction yield. The 10–13 s reactions utilized maximum microwave power (300 W) while the slower transformations were performed at constant temperature (entry 3 at 130 °C, entries 8 and 9 at 120 °C, entry 10 at 150 °C). The limited tolerance of functional groups present in the substrates was probably a consequence of interfering coordination to the cobalt metal. Alkyl fluorides (entry 5) and ethers (entries 4, 6, and 10) are non-coordinating, or only weakly coordinating to cobalt, and their presence did not reduce the yield. However the presence of alkene (entry 7), ester and alcohol functionalities instead decreased the yield drastically. The reactions of the aliphatic amines **1a** and **b** with cobalt carbonyl could also be conducted without irradiation at room temperature, but at the expense of increased reaction times and somewhat lower yields. Sterically hindered **1h**,**i**, and sluggish **1j** demanded prolonged heating to afford workable yields. Unsubstituted aniline furnished less than 5% yield according to GC–MS after 20 min at 120 °C with the standard reaction protocol. For anilines to function, an electron-donating *p*-methoxy group was needed to increase the nucleophilicity, **1j**. In entry 10, propylene carbonate was also added to stabilize the cobalt carbonyl at higher temperatures and to improve the conversion of **1j**.[18] The work-up procedure of the cold product mixture was convenient, involving simple dilution with CH_2Cl_2 and washing with hydrochloric acid (0.1 M) until it became colorless.[19] After separation, drying, and evaporation of the organic phase, pure product **2** was isolated.

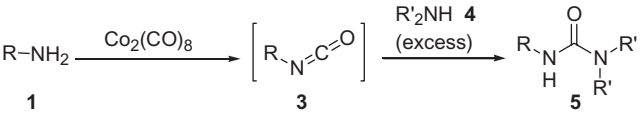
While monitoring the preparative outcome by GC–MS, small amounts of isocyanate **3** were detected in entries 1, 3, and 10 (Table 1). These observations gave rise to our mechanistic proposal with an isocyanate **3** as the key intermediate, capturing the free primary amine **1**, or alternatively, undergoing self-condensation[20] to form the urea **2** (Scheme 2). In support of the proposed isocyanate route, amine **1b** reacts immediately with preformed isocyanate **3b** in acetonitrile to afford a 93% isolated yield of urea **2b**. However, Hong and Chang have recently published an alternative mechanism based on density functional calculations and not involving free isocyanate as an intermediate.[21]



Scheme 2.

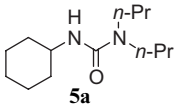
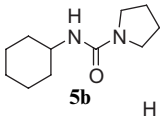
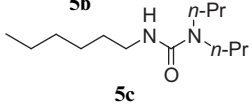
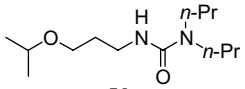
1.2. Unsymmetrical ureas

A method for direct preparation of unsymmetrical ureas without using isolated isocyanates,[22] solid-supported reactants[23,24] or sensitive phosgene equivalents would be of great synthetic value. However, when two different primary amines were used in our standard $Co_2(CO)_8$-protocol, a mixture of products was consistently formed. In order to bypass this problem, we used a primary amine **1** in combination with an excess of a secondary amine (Scheme 3).



Scheme 3.

Table 2. Rapid microwave-heated generation of unsymmetrical ureas from primary and secondary amines[a]

Entry	Amines	Time (s)	Product	Yield[b] (%)
1	**1a** + $HN(n\text{-Pr})_2$ **4a**	10	 **5a**	44 25[c]
2	**1a** +  **4b**	10	 **5b**	35
3	**1b** + **4a**	10	 **5c**	55
4	**1f** + **4a**	10	 **5d**	41

[a] Employing 1.0 equiv primary amine, 5.0 equiv secondary amine, 0.66 equiv $Co_2(CO)_8$, and 2.0 equiv triethylamine in 2.5 mL acetonitrile. Variable temp (T_{max} = 110 °C).
[b] Isolated yield based on **1** (>95% purity of **5** by GC–MS).
[c] 20 min of microwave irradiation at 130 °C.

In this way, **1** generates the corresponding isocyanate via an initial reaction with $Co_2(CO)_8$, before the nucleophilic attack by the secondary amine **4** delivers the unsymmetrical urea **5**. The preparative results are presented in Table 2, employing 10 s of heating and 5 equiv of **4**. This one-pot, two-step reaction furnished unsymmetrical ureas in workable yields (35–55%), utilizing the same quick purification protocol as described above. Notably, some of the yields of **5** were modest despite full conversion after 10 s of heating, probably as a consequence of side reactions in which the urea product competes with the secondary amine to attack the isocyanate. Possibly, the isocyanates may also react with each other upon heating, forming trimers.[25] Increasing the reaction time did not improve the outcome of these reactions but instead resulted in reduced yields (see Table 2, entry 1).

In summary, a novel and very fast gas-free carbonylation method for the preparation of ureas has been presented. By combining the power of high-density microwave heating with in situ generation of intermediate isocyanates from $Co_2(CO)_8$, amines were converted to the corresponding ureas in reaction times as short as 10 s.

1.3. General method for synthesis of symmetrical ureas from primary amines

Primary amine, (0.60 mmol), $Co_2(CO)_8$ (0.40 mmol, 137 mg), NEt_3 (121 mg, 1.2 mmol) and 2.5 mL of acetonitrile were mixed in a 5 mL vial which was immediately capped with a Teflon septum under air. The Smith microwave synthesizer was set to 250 °C, and the irradiation time to 10 or 13 s. Alternatively, the target temperature was programmed as described in Table 1. After cooling, the reaction mixture was filtered and transferred to a separating funnel. The vial was washed with 40 mL of warm CH_2Cl_2 and the organic extract was added to the separating funnel. The combined organic layer was washed with 0.1 M HCl until it became colorless. The organic layer was thereafter separated, dried (K_2CO_3) and evaporated. Products **2a**,**c**,**g**, and **j** are commercially available, while compounds **2b**,[26]**d**,[4,26]**f**,[26]**h**,[27] and **i**[28,29] are known compounds. Spectral data were in agreement with the proposed structures. Known compounds lacking literature spectroscopic data are listed below.

1.4. *N*,*N*′-Di-*n*-hexylurea 2b[26]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (br s, 2H), 3.14 (dd, J = 7.0, 5.9 Hz, 4H), 1.51–1.44 (m, 4H), 1.34–1.23 (m, 12H), 0.89–0.85 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 40.7, 31.6, 30.3, 26.7, 22.7, 14.1.

1.5. *N*,*N*′-Bis-(3-isopropoxypropyl)urea 2f[26]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (br s, 2H), 3.53 (hep, J = 6.1 Hz, 2H), 3.48 (m, 4H), 3.23 (dt, J = 6.3, 5.8 Hz, 4H), 1.72 (m, 4H), 1.12 (d, J = 6.1 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 71.6, 66.6, 39.0, 30.9, 30.1.

1.6. *N*,*N*′-Di-*tert*-butylurea 2i[28,29]

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 50.2, 29.6.

Characterization data for novel **2e** is listed below.

1.7. *N*,*N*′-Bis-(4-trifluoromethylbenzyl)urea 2e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (AA′ part of AA′XX′, 4H) 7.40 (XX′ part of AA′XX′, 4H), 4.70 (br t, J = 6.1 Hz, 2H), 4.47 (d, J = 6.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6, 80:20) δ 157.7, 143.9, 128.4 (q, J = 31.5 Hz), 126.6, 124.2 (q, J = 3.8 Hz), 123.3 (q, J = 272.0 Hz), 42.5. HRMS, ESI, ($M+H^+$): 377.1080, $C_{17}H_{15}N_2OF_6$ requires 377.1089.

1.8. General method for synthesis of unsymmetrical ureas from a primary amine and a secondary amine

Primary amine (0.50 mmol), secondary amine (2.5 mmol), $Co_2(CO)_8$ (113 mg, 0.33 mmol), NEt_3 (101 mg, 1.0 mmol), and 2.5 mL of acetonitrile were mixed in a vial which was immediately capped with a 5 mL Teflon septum under air. The Smith microwave synthesizer was set to 250 °C, and the irradiation time to 10 s. After 10 s the temperature was ca. 110–115 °C. The reaction mixture was filtered and the precipitate extracted with 40 mL of warm CH_2Cl_2. The organic extract was washed with 0.1 M HCl until it became colorless, then dried (K_2CO_3) and evaporated. Compounds **5a**[30] and **b**[31] are known compounds but are lacking earlier published ^{1}H and ^{13}C NMR spectra.

1.9. *N*-Cyclohexyl-*N*′-di-*n*-propylurea 5a[30]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (br d, J = 6.8 Hz, 1H), 3.68–3.59 (m, 1H), 3.15–3.10 (m, 4H), 1.96–1.90 (m, 2H), 1.71–1.64 (m, 2H), 1.61–1.49 (m, 5H), 1.41–1.30 (m, 2H), 1.19–1.02 (m, 3H), 0.88 (t, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 49.2, 34.1, 25.7, 25.1, 21.8, 11.5.

1.10. *N*-Cyclohexyl-*N*′-pyrrolidinourea 5b[31]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (br d, J = 6.7 Hz, 1H), 3.69–3.60 (m, 1H), 3.32–3.29 (m, 4H), 1.98–1.92 (m, 2H), 1.90–1.87 (m, 4H), 1.72–1.65 (m, 2H), 1.64–1.56 (m, 1H), 1.42–1.31 (m, 2H), 1.19–1.04 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 49.0, 45.4, 34.3, 25.7, 25.6, 25.1.

Characterization data for novel compounds **5c** and **5d** are listed below.

1.11. *N*-Hexyl-*N*′,*N*′-dipropylurea 5c

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (br s, 1H), 3.22–3.17 (m, 2H), 3.14–3.10 (m, 4H), 1.59–1.44 (m, 6H), 1.31–1.27 (m, 6H), 0.90–0.85 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 49.0, 40.8, 31.5, 30.4, 26.6, 22.5, 21.8, 14.0, 11.4. HRMS, ESI, ($M+H^+$): 229.2282, $C_{13}H_{29}N_2O$ requires 229.2280.

1.12. *N*-(3-Isopropoxypropyl)-*N*′-dipropylurea 5d

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (br s, 1H), 3.53 (hep, $J = 6.1$ Hz, 1H), 3.52–3.49 (m, 2H), 3.35–3.31 (m, 2H), 3.12–3.08 (m, 4H), 1.76–1.70 (m, 2H), 1.58–1.48 (m, 4H), 1.13 (d, $J = 6.1$ Hz, 6H), 0.86 (t, $J = 7.4$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 71.7, 68.0, 48.9, 40.1, 30.0, 22.1, 21.7, 11.3. HRMS, ESI, ($M+H^+$): 245.2227, $C_{13}H_{29}N_2O_2$ requires 245.2229.

Acknowledgements

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18. Personal communication from Professor M. Beller.
19. The acidic solution will cause the urea–cobalt complex to dissociate according to the equation below. B can either be a base or, as in our case, a urea compound. With benzylic compounds **2d** and **e**, the use of more concentrated HCl (aq) results in debenzylation. $4[[BCo(CO)_4]^+[Co(CO)_4]^-] + 8HCl \rightarrow 2H_2(g) + 8CO(g) + 3[Co(CO)_4]_2 + 2CoCl_2 + 4BHCl$. See: Wender, I.; Sternberg, H. W.; Orchin, M. *J. Am. Chem. Soc.* **1952**, *74*, 1216–1219.
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