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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.
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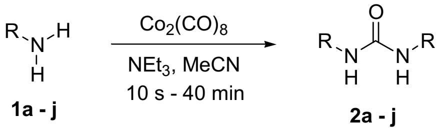
1. Introduction

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]



Scheme 1.

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 stereoselective 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

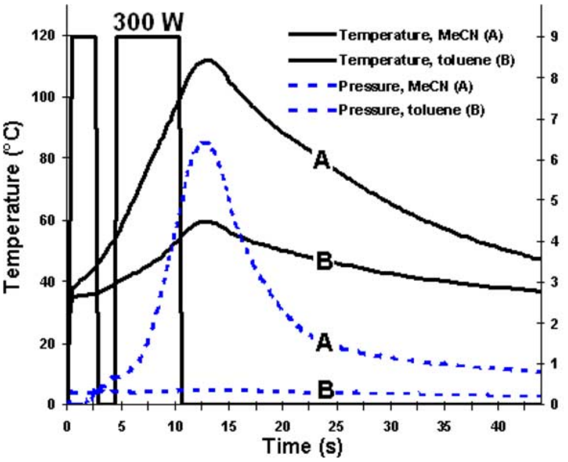


Figure 1. Temperature, power, and pressure profiles from 10 s of microwave heating (Table 1, entry 1). Note that the microwave power is divided into two separate pulses separated by 2 s.[13]

Keywords: Microwave; Carbonylation; Cobalt carbonyl; Urea; Isocyanate.

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

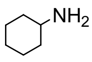
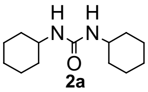
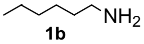
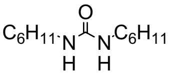
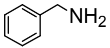
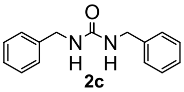
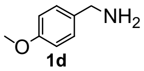
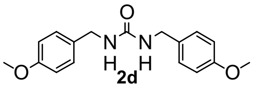
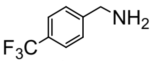
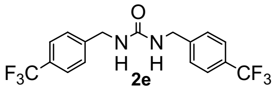
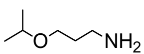
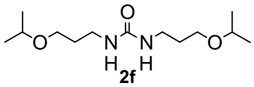
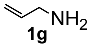
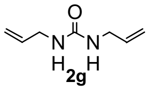
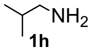
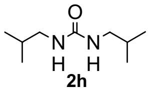
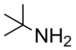
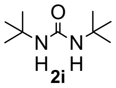
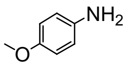
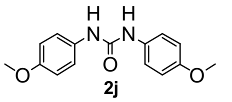
1.1. Symmetrical ureas

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.

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