NaIO₄-oxidized carbonylation of amines to ureas[†]

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Oxidative carbonylation of amines using NaIO₄ as the oxidant and NaI as a promoter affords good to excellent yields of ureas from primary amines in the absence of transition metal catalysts.

In addition to being common functional groups in pharmaceutical compounds,^{1–4} ureas are also frequently found in agricultural products and dyes.^{5–7} Traditional methods to synthesize ureas are generally based on reactions of amines with phosgene or phosgene derivatives, such as carbodiimidazole (CDI), triphosgene or *S*,*S*-dimethyl dithiocarbonate (DMDTC).^{8,9} These reactions can produce a variety of symmetrical or unsymmetrical ureas in excellent yields. However, phosgene is toxic and phosgene derivatives are undesirable from the standpoint of expense, waste minimization¹⁰ and atom economy.¹¹

Transition metal-catalyzed oxidative carbonylation of amines^{12,13} provides an alternative to phosgene and phosgene derivatives. Many metals including Pd, Ru, Rh, Au, Co, Ni and W have been employed as catalysts in the carbonylation reaction.^{12,13} However, there are also problems with metal catalysts including the expense of noble metal complexes and the possibility of heavy metal contamination in the products. Sulfur^{14–16} and selenium^{17–19} catalyzed systems are also known and avoid some of the drawbacks associated with metal catalysis. These systems, however, produce the volatile and toxic byproducts, H₂S and SeH₂, respectively.

Additional methods that avoid the presence of metal catalysts while addressing toxicity and waste stream issues would be advantageous. We now report oxidative carbonylation of amines to ureas without the addition of metal catalysts in a system using sodium periodate as the oxidant and iodide as the promoter.

In conjunction with our previous work on W(CO)₆-catalyzed carbonylation of ureas as methodology for synthesis of complex targets,^{20–23} we investigated carbonylation of amines using various combinations of oxidants, promoters and bases.²⁴ Among the oxidants studied were NaIO₄, 30% H₂O₂, I₂–FeCl₃, I₂, 4-methylmorpholine *N*-oxide and O₂. Extensive control experiments established that the W(CO)₆ catalyst was necessary to obtain high yields of the urea products, with one exception.²⁵ When the oxidant was NaIO₄ and iodide ion was present as a promoter, 4-methoxybenzylamine was converted to the corresponding urea in excellent yield, whether the W(CO)₆ catalyst was added to the reaction

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mixture or not (eqn (1)). In fact, the W(CO)₆-catalyzed version of this reaction afforded the urea in only 3% higher yield than the experiments in which no metal carbonyl had been added (84% vs. 81%). Low to negligible yields of the urea were formed when every other oxidant was reacted in the absence of the metal catalyst. These results led us to carry out optimization studies on the NaIO₄-oxidized carbonylation reaction with the goal of developing conditions that did not require the addition of a metal catalyst.



Control experiments were performed with 4-methoxybenzylamine as substrate, $H_2O-CH_2Cl_2$ as solvent and K_2CO_3 as base. Initial experiments addressed the need for the presence of both the NaIO₄ oxidant and the NaI promoter. When NaI was used in the absence of oxidant, no urea was produced under CO pressures of 45 atm. Analogously, an experiment with only NaIO₄ as oxidant but no iodide promoter yielded similar results, confirming that both components must be present in the reaction mixture.

Control experiments were carried out to investigate the possibility that iron or ruthenium carbonyl present in trace amounts in the carbon monoxide²⁶ could be catalyzing this reaction. When authentic $Fe(CO)_5$ or $Ru_3(CO)_{12}$ $(4.0 \times 10^{-5} \text{ mol}, 2 \text{ mol}\%)$ was added to a reaction of 4-methoxybenzylamine under the standard conditions, the vield of urea was similar to that obtained in the absence of the metal carbonyl complex (68% and 62%, respectively). In efforts to minimize the possibility of contamination of the CO by Fe or Ru carbonyl, the reaction was repeated with CO from an aluminium cylinder.²⁶ Fe(CO)₅ is known to be a contaminant in CO from steel cylinders, however, the use of aluminium tanks minimizes the content of Fe(CO)₅ in the CO. Using NaIO₄-NaI and K₂CO₃ as base, but with CO from the aluminium cylinder, 80% yield of bis(4-methoxybenzyl) urea was obtained. Together, these control experiments rule out catalysis by adventitious metal carbonyls.

In an additional reaction, I_2 was used as a cooxidant–iodide source in place of the NaI. This reaction did, in fact, yield complete conversion of the starting material but afforded a 1 : 1.7 ratio of urea to formamide (eqn (2)). When the solvent is CH₂Cl₂ without the addition of water as a cosolvent, only trace amounts of the urea can be detected in the ¹H NMR spectra. Failure of the reaction under these conditions is probably due to insolubility of NaIO₄ and NaI. These experiments have established that NaIO₄, a base and a source

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of iodide are required to carry out metal-free urea synthesis under these conditions.



Optimization studies using 4-methoxybenzylamine (1) led to the following conditions: 1.5 equiv. of 4-(dimethylamino) pyridine (DMAP) as base, 0.8 equiv. of NaIO₄ as oxidant and 0.5 equiv. of NaI as promoter under 45 atm of CO pressure. After 8 hours, urea 2 was obtained as an off-white powder in 81% yield. Increased temperature, pressure or time resulted in lower yield.

Optimization experiments revealed that at pressures as low as 20 atm, the urea was formed as the major product. When the experiment was conducted at 1 atm, no urea was produced but 4-methoxybenzonitrile was formed in 42% yield. Precedent for this oxidation reaction is found in the transformation of benzylamines to benzonitriles upon treatment with the Dess–Martin periodinane.²⁸ To test if the nitrile was an intermediate in urea formation, two equiv. of 4-methoxybenzonitrile were subjected to the same reaction conditions that converted 4-methoxybenzylamine to urea. This yielded no urea, leading to the conclusion that the nitrile is not an intermediate.

 Table 1
 Carbonylation of amines with NaIO₄–NaI

Several primary amines have been subjected to the NaIO₄–NaI carbonylation conditions (Table 1). Unhindered alkylamines form the urea readily under these conditions (entries 1 and 2). Sterically hindered *tert*-butylamine gives low yields (entry 4) but moderately hindered isopropyl amine still gives excellent results (entry 3). With the exception of *tert*-butylamine, yields compare favorably to those obtained using Pd²⁷ or W²³ catalysts.

Various 4-substituted benzylamines were subjected to the reaction conditions (eqn (3)). Again, excellent yields were obtained when optimized conditions were used (Table 2). When DMAP is used as the base, yields are higher than those obtained with $W(CO)_6$ as catalyst.²³ Pd catalysts produce higher yields in the reported cases,^{27,29} but the literature data are limited. Little substituent effect was observed except that more electronegative halide derivatives give slightly lower yields (entries 6–9). Interestingly, when a weaker base, K_2CO_3 , is used, proton acidities do become relevant (column 4).

$$x \xrightarrow{\text{NAIO}_4, \text{ NaI}} \underbrace{\frac{\text{NAIO}_4, \text{ NaI}}{\text{DMAP, CO}}}_{8 \text{ h, rt, CH}_2\text{Cl}_2} \xrightarrow{\text{O}} \underbrace{\text{NAIO}_4, \text{ NaI}}_{\text{M}} \xrightarrow{\text{O}} \underbrace{\text{NAIO}_4, \text{ NaI}}_{\text{M}} \xrightarrow{\text{O}} \underbrace{\text{NAIO}_4, \text{ NaI}}_{\text{M}} \xrightarrow{\text{O}} \underbrace{\text{NAIO}_4, \text{ NaIO}_4, \text{ NaIO}_4,$$

In an effort to extend these results to aromatic amines, aniline was also subjected to metal-free carbonylation conditions, but oxidation occurred in preference to carbonylation, yielding hydroquinone as the major product. This result is consistent

Entry	$RNH_2 R =$	% Yield ^{<i>a,b</i>} (Pd(0)-catalyzed) ²⁷	% Yield ^{<i>a,c</i>} $(W(CO)_6$ -catalyzed) ²³	% Yield ^{a,d} (NaIO ₄ -NaI)
l	<i>n</i> -Bu	96	78	94
2	<i>i</i> -Bu			96
3	<i>i</i> -Pr		27	91
1	t-Bu	89	62	20

^{*a*} Isolated yield per equivalent of amine. ^{*b*} Conditions: 20.0 mmol amine, 0.2 mmol PdI₂, 0.02 mmol KI, 20 mL DME, 100 °C, 16 atm CO, 4 atm air, 40 atm CO₂, 15 h. ^{*c*} Conditions: 3.6 mmol amine, 0.071 mmol W(CO)₆, 1.8 mmol I₂, 5.0 mmol K₂CO₃, 15 mL H₂O–15 mL CH₂Cl₂, 70 °C, 80 atm CO, 24 h. ^{*d*} Conditions: 2.0 mmol amine, 1.0 mmol NaI, 1.6 mmol NaIO₄, 3.0 mmol DMAP, 15 mL H₂O–15 mL CH₂Cl₂, room temperature, 45 atm CO, 8 h.

Fable 2 Carbonylation o	f 4-substituted	benzylamines
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Entry	Х	% Yield ^{<i>a</i>} (Pd(0)-catalyzed)	% Yield ^{<i>a,b</i>} (W(CO) ₆ -catalyzed) ²³	% Yield ^{<i>a,c</i>} (NaIO4–NaI K ₂ CO3)	% Yield ^{a,d} (NaIO ₄ –NaI DMAP)
1	-OMe	_	70	81	81
2	-CH ₃	$99^{29,e}$		61	78
3	-H	94 ^{27,f}	73	46	88
4	$-COOR^{g}$		55	10	85 ^h
5	$-NO_2$		76	1	79^{h}
6	-I -		_	27	87^{h}
7	-Br		77	21	78
8	C1	$87^{29,e}$	77	7	72
9	-F	_		0	72

^{*a*} Isolated yield per equivalent of amine. ^{*b*} Conditions: 3.6 mmol amine, 0.071 mmol W(CO)₆, 1.8 mmol I₂, 5.0 mmol K₂CO₃, 15 mL H₂O–15 mL CH₂Cl₂, 70 °C, 80 atm CO, 24 h. ^{*c*} Conditions: 2.0 mmol amine, 1.0 mmol NaI, 1.6 mmol NaIO₄, 3.0 mmol K₂CO₃, 15 mL H₂O–15 mL CH₂Cl₂, room temperature, 45 atm CO, 16 h. ^{*d*} Conditions: 2.0 mmol amine, 1.0 mmol NaI, 1.6 mmol NaIO₄, 3.0 mmol DMAP, 15 mL H₂O–15 mL CH₂Cl₂, room temperature, 45 atm CO, 8 h. ^{*e*} Conditions: 2.0 mmol amine, 0.0044 mmol Pd(aniline)(NHC) catalyst, 6.0 mL DMF, 31.6 atm CO, 8.0 atm O₂, 150 °C, 1 h. ^{*f*} Conditions: 20.0 mmol amine, 0.2 mmol PdI₂, 0.02 mmol KI, 20 mL DME, 100 °C, 16 atm CO, 4 atm air, 40 atm CO₂, 15 h. ^{*g*} For the W(CO)₆-catalyzed reaction, R = Et; for the NaIO₄–NaI conditions, R = Me. ^{*h*} One extra equiv. of base was added since the amine was added as the HCl salt.

with similar observations by Srivastava *et al.*³⁰ during studies on oxidation of aromatic amines using periodate.

In conclusion, conversion of amines to ureas using mild and atom economical conditions has been realized in the absence of a transition metal catalyst. These transformations take place at room temperature under CO pressures as low as 20 atm. High yields of urea have been obtained for unhindered primary alkyl amines and benzylamines. The reaction is sensitive to steric hindrance in the alkyl substituent, as evidenced by lower yields from *tert*-butylamine. The mechanism of this reaction is still under study but preliminary results suggest that a hypervalent iodine species could be responsible for the reactivity. Further research on this reaction is underway.

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