

Low-Temperature Synthesis of Tetraalkylureas from Secondary Amines and Carbon Dioxide

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Abstract: The reaction of dialkylamines with CO_2 giving tetraalkylureas can be performed at 60 °C. The reaction requires CCl_4 , is weakly promoted by DMAN or PPh₃, and is not promoted by a Pd catalyst. A two-step procedure, in which dialkylammonium dialkylcarbamate is produced in situ and then reacted with CCl_4 and free dialkylamine, gave greater yields of urea than a simple single-stage procedure.

Carbon dioxide fixation offers the potential of replacing syntheses based upon toxic carbon monoxide or phosgene while simultaneously taking advantage of the abundance of waste CO_2 . Literature studies describe a range of reactions of CO₂, including dialkylureas from primary amines and CO_2 .¹⁻¹² Unfortunately, the preparation of tetraalkylureas from CO₂ and secondary amines has been more difficult.^{2,13} Fichter et al. found that the tendency of the carbamates of ammonia and primary amines to be dehydrated to the corresponding ureas was not observed with the carbamates of secondary amines.^{1,2,14} The transformation has been achieved but with both catalysis and elevated temperatures (120-250 °C).^{10,15} At moderate temperatures (i.e., below 100 °C), the only published synthesis using CO₂ required large concentrations of PdCl₂(MeCN)₂ catalyst and a stoichiometric

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amount of triphenylphosphine in CCl_4 /MeCN solvent (eq 1).¹⁶ The highest yield of urea was 7 turnovers (mol of urea per mol of Pd). We initially chose to investigate this system to determine whether the catalytic efficiency could be increased and whether the reaction could be performed with a substoichiometric quantity of the phosphine.

$$2NHR_2 + CO_2 \xrightarrow{PdCl_2(MeCN)_2 / PPh_3} R_2N \xrightarrow{V} NR_2 + H_2O$$
(1)

Experimental Section

Materials and Methods. All chemicals were obtained from commercial sources and used directly without further purification. The CO₂ was industrial grade obtained from Praxair. Most of the experiments were carried out under air, except as noted. THF and toluene were dried and distilled from sodium/benzophenone ketyl, and MeCN and DMSO were dried by stirring with Na₂SO₄. The yield of tetraalkylurea was calculated by ¹H NMR integration relative to CH₂Cl₂ as an internal standard. The identification of the product was confirmed by comparison of the ¹H NMR spectrum to that of the commercially available tetraalkylurea (1,1,3,3-tetraethylurea, 1,1,3,3-tetrabutylurea, or bis(pentamethylene)urea) and published spectra^{17–19} and by checking that no new peaks or line broadening were observed in the spectrum of a mixture of the obtained product and the commercially available sample.

Single-Step Method for the Preparation of Tetraethylurea. Experiments were carried out by combining 10 mL of solvent with 2 mmol of NHR₂ and 1 mmol of DMAN in a 35 mL glass vial with a stir bar, under the pressure of CO_2 indicated in the tables, and then heating to 60 °C for 24 h.

Two-Step Method for the Preparation of Tetraalkylurea. In the first step of this procedure, 10 mL of solvent, 1 mmol of HNR₂, and 1 mmol base (if used) and a stir bar were placed into a 35 mL glass vial and stirred under 1 bar of CO_2 at room temperature for 1 h. Subsequently, the vial was opened to air and 1 mL of CCl₄ and another 1 mmol of HNR₂ were added. The vial was heated and stirred, with an empty balloon on the top of the vial, at 60 °C for 23 h, except as noted.

Isolation of Tetraalkylurea. Although the yield data in the tables are spectroscopic yields, the isolated yields were also determined. For example, isolation of tetrabutylurea from the product mixture was achieved by evaporating the volatiles under vacuum, adding 3 M HCl_(aq) to the residue, and extracting several times with ether. Removal of the ether from the dried extract gave the product, tetrabutylurea, in 62% yield, as confirmed gravimetrically and by ¹H NMR spectroscopy. For bis(pentamethylene)urea and tetraethylurea (both prepared in MeCN), the isolated yields were 71 and 35%, respectively.

Results and Discussion

During an evaluation of the Pd-catalyzed synthesis of tetraalkylureas from dialkylamines and CO_2 (eq 1), we compared single-step and two-step procedures. In the

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 $\label{eq:conversion} \begin{array}{l} TABLE \ 1. \quad Conversion \ of \ Diethylamine \ and \ CO_2 \ to \\ Tetraethylurea \end{array}$

entry	[PdCl ₂ (MeCN) ₂] (mmol)	PPh ₃ (mmol)	procedure ^a	urea yield ^b (%)
1	0	0.3	В	44
2	0.1	0	В	17
3	0.1	0.3	Α	11
4	0.1	0.3	В	45
5	0	0	В	34

^{*a*} Procedures. (A) One-Step Procedure: 10 mL of THF with 2 mmol of NHEt₂, 1 mL of CCl₄, under 1 bar of CO₂ as indicated, heat to 60 °C for 24 h. (B) Two-Step Procedure: (step 1) 10 mL of THF with 1 mmol of NHEt₂ under 1 bar of CO₂ for 1 h at rt; (step 2) remove CO₂, heat to 60 °C, add 1 mL of CCl₄ and 1 mmol of NHR₂ stirring for 23 h. ^{*b*} Percentage of theoretical yield, as determined spectroscopically.

single-step procedure, the dialkylamine, CCl_4 , Pd catalyst precursor, and PPh₃ were heated together in solvent under 1 bar of CO₂ for 60 °C for 1 day. In the two-step procedure (eq 2, where base = NHR₂), 1 mmol of the dialkylamine in the presence of the Pd complex and PPh₃ was exposed to CO₂ for 1 h to convert the amine to the carbamate, after which the CO₂ source was removed and the carbamate was reacted with a second mmol of dialkylamine and excess CCl₄. The carbamate was observed after the first step by ¹H NMR spectroscopy. Compared to the single-step procedure, the two-step procedure gave greater yields of tetraalkylurea (entries 3 and 4 in Table 1).

$$\mathsf{NHR}_2 + \mathsf{CO}_2 \xrightarrow{\mathsf{Base}} \mathsf{R}_2 \mathsf{N} \xrightarrow{\mathsf{O}} \mathsf{O}^{-} {}^{+}\mathsf{H}\mathsf{Base} \xrightarrow{\mathsf{NHR}_2} \mathsf{R}_2 \mathsf{N} \xrightarrow{\mathsf{O}} \mathsf{NR}_2 + \mathsf{H}_2 \mathsf{O} \quad (2)$$

Note that these experiments were performed in THF solvent, rather than acetonitrile, because all attempts to use the Pd catalyst for this reaction in acetonitrile resulted in the formation of not only urea but also significant quantities of an unidentified salt.

The effect of the amount of phosphine and Pd catalyst on the urea synthesis was measured using the two-step procedure in THF. First, we noted that the Pd catalyst has no beneficial effect (compare runs 2 and 5 and runs 4 and 1). However, the yield of tetraalkylurea is improved in the presence of PPh₃ (compare runs 1 and 5 and runs 2 and 4). Therefore, it is not necessary to add the Pd catalyst, but the phosphine alone has some weak ability to promote the reaction. The Pd catalyst was omitted in all subsequent experiments, giving the added advantage that the occurrence of *N*,*N*-diethylformamide as a minor byproduct, as observed by both Morimoto¹⁶ and ourselves when using the published method, is suppressed.

Other bases were also tested for their ability to promote the reaction in the absence of Pd and PPh₃. Although the promoting effect is moderate, the greatest effect was found with DMAN (1,8-dimethylaminonaphthalene, Table 2). Other amines did not affect the yield significantly, probably because they are no stronger than diethylamine as bases. The combination of the two-step procedure with the use of DMAN gave tetraethylurea yields of 55-64% (Table 3). The corresponding reaction of CO₂ with piperidine and dibutylamine gave bis-(pentamethylene)urea and 1,1,3,3-tetrabutylurea in high yield.

 TABLE 2. Effect of Added Bases on the Synthesis of Tetraethylurea^a

base	NHEt ₂ :base	urea yield ^b (%)
no extra base added	na	34
DMAN	2:1	55
	20:1	43
NEt ₂ Ph	2:1	36
	20:1	32
NPh ₃	2:1	30
	20:1	22
NEt ₃	2:1	36
	20:1	25

^{*a*} Procedure: (step 1) 10 mL of solvent with 1 mmol of NHEt₂ and 1 or 0.1 mmol of base (where used), under 1 atm of CO_2 for 1 h at room temperature; (step 2) remove CO_2 , heat at 60 °C, add 1 mL of CCl₄ and 1 mmol of NHEt₂ stirring for 23 h. ^{*b*} Percentage of theoretical yield, as determined spectroscopically.

TABLE 3. Conversion of Dialkylamine and CO_2 to Tetraalkylurea in the Presence of DMAN

entry	amine	procedure ^a	Т (°С)	CO ₂ (bar)	solvent	t (h)	urea yield ^b (%)
1	NHEt ₂	Α	60	1	THF	24	33
2	NHEt ₂	Α	60	50	THF	24	0
3	NHEt ₂	В	rt	1	THF	24	20
4	NHEt ₂	В	60	0	THF	24	0
5	NHEt ₂	В	60	1	THF	2	14
6	NHEt ₂	В	60	1	THF	24	55
7	NHEt ₂	В	60	1	THF	72	62
8	NHEt ₂	В	60	1	MeCN	24	64
9	NHEt ₂	В	60	1	DMSO	24	0
10	NHEt ₂	В	60	1	toluene	24	32
11	NHEt ₂	В	70	1	THF	24	34
12	piperidine	В	60	1	THF	24	53
13	piperidine	В	60	1	MeCN	24	72
14	NHBu ₂	В	60	1	THF	24	99

^{*a*} Procedures: (A) One-Step Procedure: 10 mL of solvent with 2 mmol of NHR₂, 1 mL of CCl₄, and 1 mmol of DMAN, under the pressure of CO₂ as indicated, heat for 24 h. (B) Two-Step Procedure: (step 1) 10 mL of solvent with 1 mmol of NHR₂ and 1 mmol of DMAN, under 1 bar of CO₂ for 1 h at room temperature; (step 2) remove CO₂, heat at the temperature indicated, add 1 mL of CCl₄ and 1 mmol of NHR₂ stirring for 23 h. ^{*b*} Percentage of theoretical yield, as determined spectroscopically.

The two-step procedure was designed to ensure that a fair concentration of free dialkylamine (neither carboxylated nor protonated) was present in solution during the reaction. Tests of the single-step procedure showed that at very high CO_2 pressures, under which conversion of the amine to the carbamate salt would be expected to be complete, no urea was formed (Table 3, compare entries 1 and 2).

The conversion of dimethylamine to tetramethylurea in CCl_4 as an undesired side reaction was noticed by White et al.,²⁰ although they did not recognize that CO_2 from the air was the carbonyl source. That the reaction is indeed a fixation of CO_2 has now been demonstrated by performing the reaction under nitrogen using degassed reagents and solvent. For this experiment, the two-step procedure (Table 3, entry 4) was followed, with the exception that no CO_2 was present. Neither tetraethylurea nor diethylformamide was produced.

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The tetraethylurea yield was affected by reaction temperature and solvent. Although the temperature effect (entries 3, 6, and 11) is not yet understood, the greater yield at 60 °C compared to that at 70 °C may be related to the fact that the decomposition temperature of the carbamate salt is 62-63 °C.²¹ Among the solvents tested, acetonitrile allows the best yield of urea and only gave the undesired salt if the Pd catalyst was present. THF also gave fair results, but the yield was significantly lower in DMSO and toluene.

Other halide sources are not nearly as effective as CCl_4 for the urea synthesis. After testing CBr_4 , CH_2Cl_2 , $CHCl_3$, MeI, HCl (as $[NH_2Et_2]Cl$), $CCl_3C(O)CCl_3$, and *tert*-butyliodide as alternative halide sources, only CBr_4 was found to be effective, producing urea at a yield of 38% but with a large amount of an unidentified product. In the absence of any halide source, no tetraethylurea was produced. The role of the halide source is not yet known, but CCl_4 in combination with Lewis bases is known to react with carbonyl compounds to give CCl_3 -subsituted alcohols.²² One could then speculate that such a reaction on diethylcarbamic acid would generate a CCl_3 -substituted intermediate that would be more reactive to nucleophilic attack by amine.

Conclusions

The reaction of dialkylamines with CO_2 giving tetraalkylureas requires CCl_4 , is weakly promoted by DMAN or PPh₃, and is not promoted by a Pd catalyst. The use of a two-step procedure, in which dialkylammonium dialkylcarbamate is produced in situ and then reacted with CCl_4 and free dialkylamine, gave greater yields of urea than mixing all reagents together at the same time.

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