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Debenzylation of Tertiary Amines Using Phosgene or Triphosgene: An Efficient and Rapid Procedure for the Preparation of Carbamoyl Chlorides and Unsymmetrical Ureas. Application in Carbon-11 Chemistry

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Efficient and rapid preparations of carbamoyl chlorides and unsymmetrical ureas from tertiary amines and phosgene or its safe equivalent triphosgene [bis(trichloromethyl)carbonate, BTC] are described. First, the reaction of stoichiometric amounts of phosgene with secondary amines was revisited, and it was shown that the formation of carbamoyl chlorides in high yields required careful adjustments of experimental conditions and the use of pyridine as an HCl scavenger. A phosgene-mediated dealkylation of triethylamine was observed when this base was used instead of pyridine. Taking advantage of this observation, a strategy of synthesis of carbamoyl chlorides from tertiary amines and phosgene has been developed. *N*-Alkyl-*N*-benzyl(substituted)tetrahydroisoquinolines, -piperazines, -piperidines, or -anilines were treated with stoichiometric amounts of phosgene (or BTC) in CH_2Cl_2. Tertiary amines bearing electron-enriched benzyl group(s) afforded carbamoyl chlorides in excellent yields and without any contamination by symmetrical ureas. Subsequent additions of primary or secondary amines to these carbamoyl chlorides produced unsymmetrical ureas in single-pot and high-yielding operations. This methodology was applied in ^{11}C-chemistry. From [^{11}C]phosgene, a common precursor used in the preparation of radiotracers for positron emission tomography, a rapid and efficient synthesis of ^{11}C-carbamoyl chlorides and ^{11}C-unsymmetrical ureas derived from tetrahydroisoquinoline and piperazine is described. The first example of ^{11}C-amide formation from the reaction of a ^{11}C-carbamoyl chloride and an organometallic (cyanocuprate or a Grignard reagent in the presence of a nickel catalyst) is also presented.

Introduction

Radiolabeled tracers play a critical role throughout the drug discovery process and medical imaging. They are used in pharmaceutical research in screening against new targets for labeling novel enzymes or receptors and for plasma protein binding experiments. During the lead optimization stage, radiolabeled drug candidates are useful for the identification of circulating metabolites, determination of drug absorption, distribution, metabolism, and excretion. In the field of nuclear medicine, positron emission tomography (PET) is a noninvasive technique and a method of choice to provide anatomical distribution and localization of radiolabeled drugs in living human organs, especially the brain.[1] The radioisotopes of carbon, ^{14}C in pharmaceutical research and ^{11}C in positron emission tomography (PET), are valuable radionuclides since they permit the synthesis of radiolabeled versions of the compound of interest. The syntheses with these radioisotopes share several common features: limited number of labeled precursors, submicromolar amounts of these starting materials, and a need for the introduction of the radioisotope as late as possible in the synthesis. All these reasons have restricted complex radiosyntheses. Whereas carbon-14 radiotracers or reagents[2] can be stored indefinitely with no loss of radioactivity (^{14}C-half-life: 5700 years), the short half-life of carbon-11 (20 min) requires the rapid preparation and purification of carbon-11 labeled molecules. Those have to be carried out immediately before use and from cyclotron produced precursors ([^{11}C]CO_2, [^{11}C]CO, or [^{11}C]CH_4) or rapidly prepared from them ([^{11}C]CH_3I, [^{11}C]$COCl_2$, [^{11}C]HCN).[3] Because of the increased molecular complexity and diversity of biologically active compounds, there is still a need for new methodologies which

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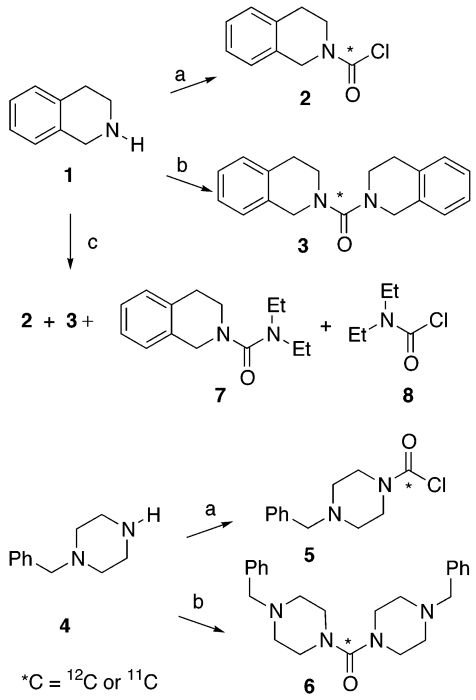
give access in short time and high yield to radioactive $^{11}C-$ or ^{14}C-probes.

Pharmaceutically active molecules often contain ureas, carbamates, or related functions. In stable isotope chemistry, carbamoyl chlorides are common intermediates for the introduction of these functional groups.[4] Moreover, they can also be transformed into amides by reaction with aryllithiums.[5] Recently, we have developed their nickel-catalyzed cross-coupling reactions with Grignard reagents as an alternative route to amides.[6] Carbamoyl chlorides are often synthesized by reaction of a secondary amine with an excess of phosgene.[7] These conditions are detrimental to the environment, and they cannot be used under radioactive conditions. Moreover, they often lead to byproducts. The pallado-catalyzed carbonylation of chloramines[8] or selenium-mediated carbonylation of amines or alcohols[9] under carbon monoxide pressure could be envisaged. However, this possibility was not considered since it required either a pressure of carbon monoxide or, in carbon-11 chemistry, a special technology.[10] Formamides are also direct precursors of carbamoyl chlorides by reaction with a chlorinating reagent,[11] but their ^{11}C-labeled counterparts have not yet been described. Methods based on the use of carbon dioxide and again a chlorinating agent have been employed both in ^{14}C-carbon[12] and ^{11}C-carbon[13] chemistries. However, yields and selectivities remained moderate. [^{11}C]Phosgene, easily prepared from cyclotron-produced [^{11}C]methane,[14] remains the precursor of choice for rapid and efficient radiosyntheses of symmetrical[15] or cyclic ^{11}C-ureas[16] and

SCHEME 1[a]



[a] Reagents and conditions: (a) excess $COCl_2$, rt, toluene; (b) [^{11}C]$COCl_2$, −78 °C, THF; (c) BTC or $COCl_2$ and NEt_3, dichloromethane.

^{11}C-carbamates via the formation of the corresponding ^{11}C-isocyanates under high dilution of the starting amine.[17] [^{11}C]Phosgene was used to prepare ^{11}C-labeled ethylchloroformate in low yields,[18] [^{11}C]methanol being preferred for the ^{11}C-labeling of methylchloroformate.[19] To our knowledge, only one ^{11}C-carbamoyl chloride has been isolated and characterized due to the low reactivity of the used amine.[20] Indeed, if carbamoyl chlorides are the products formed by reaction of secondary amines and phosgene under normal conditions,[21] ^{11}C-ureas are the only products isolated in ^{11}C-chemistry. Our preliminary labeling experiments confirmed the difficulty in preparing ^{11}C-labeled carbamoyl chlorides. The reaction of tetrahydroisoquinoline **1** or *N*-benzylpiperazine **4** (1.5 mmol or 15 μmol) in THF or toluene (400 μL) with [^{11}C]-phosgene was performed at −10 or −78 °C for 5 min. Radio-TLC or HPLC analyses of the crude reaction mixture showed the exclusive formation of the corresponding ^{11}C-ureas **3** or **6** (Scheme 1).

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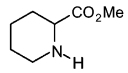
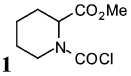
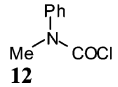
TABLE 1. Reaction of BTC with Secondary Amines: Influence of the Added Base

entry	amine[a]	base	equiv	solvent	*T* (°C)	time[b] (h)	products	relative ratio (%)[c]
1	**1**	NEt_3	2.2	THF	−78 to 20	0.15 then 16	**2**/**3**/**8**/**7**	46/0/54/0
2	**1**	NEt_3	2.2	THF	20	0.10 then 1.25	**2**/**3**/**8**/**7**	93/7/traces/0
3	**1**	NEt_3	2.2	CH_2Cl_2	20	0.25 then 1	**2**/**3**/**8**/**7**	9/46/38/7
4	**1**	NEt_3	2.2	CH_2Cl_2	20	1 then 3	**2**/**3**/**8**/**7**	4/44/38/14
5	**1**	Na_2CO_3	1	CH_2Cl_2	0	30 then 0.75	**2**/**3**	84/16
6	**1**	Na_2CO_3	1	CH_2Cl_2	−78	0.15 then 2	**2**/**3**	78/22
7	**1**	Na_2CO_3	1	THF	20	0.3 then 2	**2**/**3**	84 (68)/16
8	**1**	C_5H_5N	2.2	CH_2Cl_2	20	0.5 then 3	**2**/**3**	100/0
9	**1**	C_5H_5N	2.2	CH_2Cl_2	−78 to 20	0.16 then 3	**2**/**3**	100 (88)/0
10[d]	**1**	C_5H_5N	1.2	CH_2Cl_2	20	2 then 2	**2**/**3**	82 (60)/18
11	**4**	C_5H_5N	1.2	CH_2Cl_2	0	0.15 then 1	**5**	100 (48)/0
12	 **9**	C_5H_5N	2.5	CH_2Cl_2	20	0.15 then 1	 **10**	(81)[e]
13	 **11**	C_5H_5N	2.5	CH_2Cl_2	−50	0.15 then 1	 **12**	(60)

[a] All of the reactions were carried out with BTC (0.37 equiv) except entry 1 (reaction with phosgene): To BTC in CH_2Cl_2 at a given temperature were added the base then the secondary amine over a given period of time. After reaction, the mixture was hydrolyzed with 1 N HCl and extracted with CH_2Cl_2. [b] Time of addition followed by the reaction time. [c] Percentage of the reaction products determined by ^1H NMR. The isolated yields are given in parentheses. [d] BTC was added to the amine. [e] Crude yield, carbamoyl chloride **10** decomposed on silica gel.

As a part of our program on the synthesis of cholinergic radioligands[20,22] and the search for new ^{11}C-labeled precursors or new methodologies usable in radiolabeling[23] we have developed a rapid, efficient, and selective method to prepare carbamoyl chlorides from tertiary amines using triphosgene in stable isotope chemistry and [^{11}C]-phosgene under radioactive conditions. Applications to the synthesis of unsymmetrical ureas, carbamates, and amides in both types of chemistry are described as well.

Results and Discussion

Since conventional spectroscopic analysis of ^{11}C-labeled molecules is not possible, a new radiotracer is usually characterized by comparison of its radio-TLC or HPLC properties with those of the stable isotope reference compounds.[3] Therefore, an efficient synthesis of unlabeled carbamoyl chlorides **2** and **5** as model compounds was developed. Tetrahydroisoquinoline **1** was first chosen as a substrate because it offers several advantages: its structure is frequently encountered in biologically active compounds, it has a high boiling point, and the presence of an aromatic ring allows for reaction monitoring and analysis by TLC and HPLC. Finally, the corresponding carbamoyl chloride **2** is reasonably stable in aqueous conditions and can be purified by chromatography on silica gel without any loss. It has been prepared by reaction of amine **1** with an excess of phosgene in toluene solution in the presence of an excess of triethylamine. Using these conditions, the carbamoyl chloride **2** was contaminated with another product which was later identified as diethylcarbamoyl chloride **8** (Scheme 1, Table 1, entry 1). Because some carbamoyl chlorides are unstable and are best used without any purification, we searched for a cleaner and more efficient reaction. After a quick survey of the literature, triphosgene [bis(trichloromethyl)carbonate, BTC], a solid and safe surrogate of phosgene, appeared as the reagent of choice for preparing carbamoyl chlorides.[24]

Amine **1** was slowly added to a solution of 0.35−0.40 equiv of BTC (equal to a slight excess of phosgene) in THF or CH_2Cl_2 in the presence of a base (triethylamine, sodium carbonate, or pyridine). Table 1 presents the results as the ^1H NMR ratio of the four products eventually detected in the crude mixture: carbamoyl chloride **2** and three side compounds, ureas **3** and **7** and dialkylcarbamoyl chloride **8**. Urea **3** was the major expected byproduct in both experiments conducted with triethylamine in CH_2Cl_2 (Table 1, entries 3 and 4). Using this organic base, carbamoyl chlorides **8** and unsymmetrical ureas **7** coming from the dealkylation of the tertiary base were formed (Table 1, entries 1, 3, and 4). The specific reaction between phosgene and triethylamine, already described,[25] has been rarely mentioned as a side reaction by authors using the same conditions as ours. Heterogeneous conditions carried out with sodium carbonate generated carbamoyl chloride **2** in 68% isolated yield, without avoiding the formation of urea **3** (Table 1, entries 5−7). Pyridine, which was the base used originally with BTC,[26] gave the best result. Comparison of entries 1, 2 and 8, 9 (Table 1) shows that both triethylamine and the secondary amine **1** gave the corresponding carbamoyl chlorides (**8** and **2**, respectively) when the reagents were mixed at −78 °C. In the presence of triethylamine, the distribution of the products was strongly dependent on the temperature. At 20 °C, no carbamoyl chloride **8** was detected whereas tetrahydroisoquinoline urea **7** was formed. Such an influence of the temperature was not

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observed when the reaction was performed in the presence of pyridine in dichloromethane.

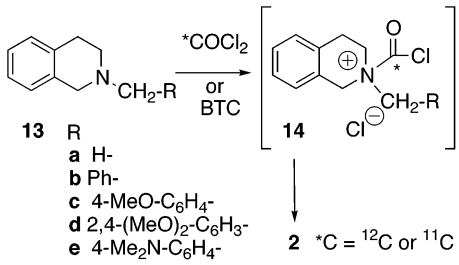
The reaction can be performed cleanly by slowly adding tetrahydroisoquinoline **1** to a mixture of BTC and pyridine in CH_2Cl_2, for example, to isolate carbamoyl chloride **2** in 88% yield on a 17 g scale experiment (entry 9). The addition order of the reagents is critical for the sole formation of the carbamoyl chloride as shown by entry 10. Under the best conditions (entry 11), *N*-benzylpiperazine **4** led quantitatively to carbamoyl chloride **5** which was isolated in 48% yield after column chromatography. This low yield is due to the partial instability of the carbamoyl chloride **5** on silica gel. Two more carbamoyl chlorides **10** and **12**[27] were synthesized according to the same conditions from amines **9**, **11**, and BTC.

The whole results presented in Table 1 show that the synthesis of carbamoyl chlorides from secondary amines and BTC in the presence of a base, often considered as a straightforward reaction, requires careful adjustments in order to avoid contamination by the corresponding ureas. The formation of diethylcarbamoyl chloride **8**, when the reaction was carried out in the presence of triethylamine, demonstrates that a tertiary amine can be dealkylated by phosgene to generate a carbamoyl chloride. This latter was unreactive toward the tertiary amine as proved by entries 3 and 4 where diethylcarbamoyl chloride **8** did not react with the excess of triethylamine to give tetraethylurea. This observation is crucial when considering the experimental conditions in radioactive chemistry where the ^{11}C-labeled carbamoyl chloride will be generated in the presence of a large excess of the starting amine. We then focused our efforts on the possible generation of carbamoyl chlorides from phosgene (or BTC) and tertiary amines.

Phosgene-Mediated Dealkylation of Tertiary Amines. Dealkylations of tertiary amines are usually performed under the von Braun conditions[28] or using acid chlorides or alkyl chloroformates.[29] Vinyl chloroformate and chloroethyl chloroformate have proved to be more selective and produce cleaner reaction products.[30] Beside dealkylation of triethylamine,[25] we found only a few reports on phosgene-induced dealkylation,[31] often demethylation,[32] of particular tertiary amines with the aim of generating a secondary amine, or to cleave a cyclic tertiary amine.[33] The possibility of using triphosgene for debenzylation of tertiary amines has been reported recently.[34]

From a mechanistic point of view, the reaction can be viewed as a two-step reaction. First, phosgene reacts

SCHEME 2



rapidly with the nitrogen lone pair of the tertiary amine to afford an acylammonium chloride. Then decomposition of this ionic intermediate to the carbamoyl chloride and alkyl chloride occurs either by an SN_1 process when allyl, benzyl, or tertiary groups are present or, more generally, by an SN_2 process.[35]

We undertook our study using the same amine, tetrahydroisoquinoline **1**, which was converted into several tertiary amines, the methyl, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 4-dimethylaminobenzyl derivatives **13a**−**e**, to test the dealkylation using phosgene or BTC (Scheme 2), its selectivity, and to choose the substrate the most favorable in terms of time and efficiency. The synthesis of these starting materials was carried out according to standard procedures.[36] Table 2 summarizes the different conditions of stoichiometry, solvent, temperature, and time. The crude mixtures were analyzed by ^1H NMR, and the proportions of the chemical species which were detected and characterized are reported. It should be noted that none of the starting amines were present in the final mixtures, even when the stoichiometry phosgene/amine was 1/1.

N-Methyl- and *N*-benzylamines **13a** and **13b** reacted immediately with phosgene (or its equivalent BTC) to form the corresponding quaternary ammonium salts **14a** or **14b**, insoluble (or slightly soluble) in toluene, ether, and THF and soluble in dichloromethane. From the reactions with *N*-methylamine **13a**, dichloromethane was the best solvent but the proportion of the carbamoyl chloride **2** reached only 54% of the mixture. Increasing reaction time and/or temperature and adding a chloride salt did not improve significantly the conversion. A competitive attack of the chloride anion on the benzylic position of the ring system was not observed as it was in the case of phthalideisoquinoline alkaloids treated with thiophosgene.[37] However, our results compare well with the phosgene-mediated rearrangement of a benzoquinolizidine where the dealkylation was governed by stereoelectronic factors.[33]

When *N*-benzylamine **13b** in CH_2Cl_2 was treated with phosgene (Table 2, entry 10), the ammonium salt **14b**

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(36) See the Supporting Information for complete experimental procedures and characterization data for all new compounds.

(37) Baradarani, M. M.; Prager, R. H. *Tetrahedron Lett.*, **1999**, *40*, 7403−7406.

TABLE 2. Dealkylation of Tertiary Amines 13 Using Phosgene or BTC

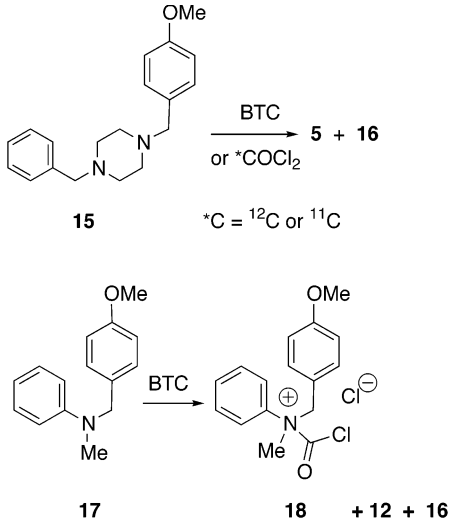
entry[a]	amine	reagent	ratio amine/reagent[b]	solvent	*T* (°C)	time (h)	**14**[c] (%)	**2**[c] (%)
1	**13a**	BTC	1/0.4	Et_2O	20	1	97	3
2		BTC	1/0.4	Et_2O	20	18	96	4
3		BTC	1/0.4	THF	20	1	93	7
4		BTC	1/0.4	THF	68	24	80	20
5		BTC	1/0.4	THF	68	24	81[d]	19
6		BTC	1/0.4	CH_2Cl_2	20	1	57	43
7		BTC	1/0.4	CH_2Cl_2	20	21	46	54
8		BTC	1/0.4	CH_2Cl_2	20	360	48	52
9	**13b**	$COCl_2$	1/1	Toluene	20	18	99	1
10		$COCl_2$	1/1	CH_2Cl_2	20	1	47	53
11		$COCl_2$	1/1	$(ClCH_2)_2$	20	1	75	25
12		$COCl_2$	5/1	THF	20	1	0	100
13	**13c**	$COCl_2$	1/1	THF	20	0.16	1	99
14		$COCl_2$	1/1	CH_2Cl_2	20	1	0	100 (65)
15		$COCl_2$	1/1	CH_2Cl_2	20	1	0	100 (65)
16		BTC	1/0.4	CH_2Cl_2	20	0.5	0	100 (60)
17	**13d**	BTC	1/0.4	CH_2Cl_2	20	0.5	0	100 (85)
18	**13e**	BTC	1/0.4	CH_2Cl_2	20	0.5	0	100

[a] To a mixture of tertiary amine in CH_2Cl_2 was added BTC in dichloromethane. The mixture was stirred for a given period of time and at a chosen temperature. The crude product was extracted with CH_2Cl_2. For practical reasons, phosgene was added to the amine. [b] Molar ratio amine/BTC. [c] Percentages of compounds **14** and **2** measured in the crude ^{1}H NMR mixture. The isolated yields are given in parentheses. [d] Addition of LiCl (30 equiv).

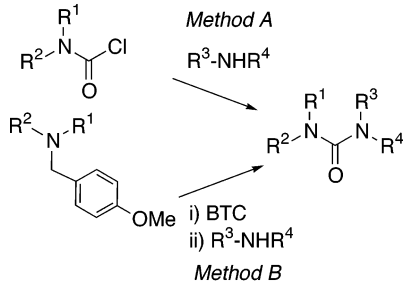
and the expected product **2** were formed in proportions similar to those observed for *N*-methylamine **13a**. Using a 5-fold excess of starting amine over phosgene (entry 12), the conversion into the carbamoyl chloride **2** was quantitative in less than 1 h. No trace of the salt **14b** was detected by ^{1}H NMR. As anticipated, the excess starting tertiary amine did not react with the carbamoyl chloride to produce the symmetrical urea. Appending electron-donating groups on the benzyl group facilitated the cleavage.[38] The 4-methoxy-, 2,4-dimethoxy-, and 4-dimethylaminobenzyl derivatives **13c**, **13d**, and **13e** were all converted directly to the carbamoyl chloride **2** using a stoichiometric amount of phosgene, and it was not possible to isolate the phosgene adduct **14**. In one case, after a short reaction time (10 min, entry 13) traces of the salt **14c** could be visualized on the ^{1}H NMR spectrum. This in good agreement with an SN_1-type of mechanism where electron-rich aromatics stabilize a benzylic carbocation and therefore increase the rate of the overall process. The reaction was fast and reproducible leading to the carbamoyl chloride **2** in isolated yields of ranging from 60 to 85%, similar to those obtained using tetrahydroisoquinoline **1**, BTC, and pyridine.

The selectivity of the reaction was tested with the piperazine derivative **15** treated with BTC in CH_2Cl_2. After 1 h at rt, only the cleavage of the 4-methoxybenzyl group was observed by ^{1}H NMR along with the formation of 4-methoxybenzyl chloride **16** (Scheme 3). The resulting carbamoyl chloride **5** was isolated in 53% yield after purification on silica gel, with a yield similar to that obtained previously from piperazine **4** (see Table 1, entry 11). The limitation of the tertiary amine dealkylation was evaluated by using a less nucleophilic amine. The aniline **17** reacted completely with BTC to afford after 30 min a 64/36 mixture of the carbamoyl chloride **12** and the salt **18**. The former was isolated with a 44% yield. Optimization of the conditions would require in this particular case the presence of a dimethoxy-, trimethoxy-, or dimethylaminobenzyl group for an efficient transformation into

SCHEME 3



SCHEME 4

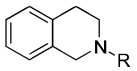
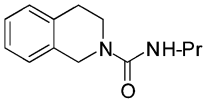
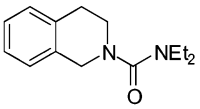
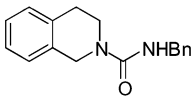
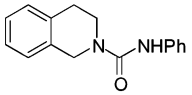
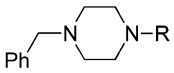
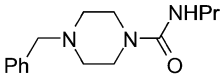
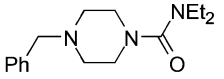
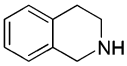
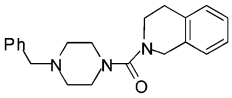
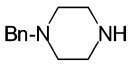
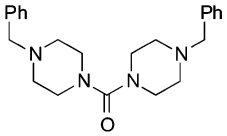
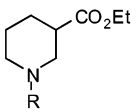
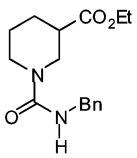
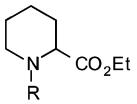
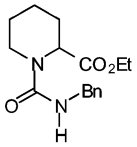


carbamoyl chloride **12** by reaction with phosgene. In view of these results it became clear that electron-enriched benzyl groups are well suited as cleavable groups from tertiary amines by triphosgene. By comparison, the benzyl moiety is not always easily removed from a tertiary amine (Table 2, entry 10) unless an excess of amine versus phosgene was used (Table 2, entry 12).[34b]

Triphosgene has been used previously for the preparation of unsymmetrical ureas either from primary[39] or

(38) Miller, M. W.; Vice, S. F.; McCombie, S. W. *Tetrahedron Lett.* **1998**, *39*, 3429−3432.

TABLE 3. Comparaison of Methods A and B To Synthesize Ureas

Entry	Starting material	R		Amine	Urea		Method	Yield %[a]
1		COCl	**2**	Pr-NH_2		**19**	A[b]	95
2		CH_2-C_6H_4-OMe	**13c**				B[c]	91
3	"	COCl	**2**	Et_2NH		**7**	A	93
4		CH_2-C_6H_4-OMe	**13c**				B	89
5	"	COCl	**2**	Bn-NH_2		**20**	A	78
6		CH_2-C_6H_4-OMe	**13c**				B	83
7	"	COCl	**2**	Ph-NH_2		**21**	A	71
8		CH_2-C_6H_4-OMe	**13c**				B	72
9		COCl	**5**	Pr-NH_2		**22**	A	79
10		CH_2-C_6H_4-OMe	**15**				B	96
11	"	COCl	**5**	Et_2NH		**23**	A	81
12		CH_2-C_6H_4-OMe	**15**				B	93
13	"	COCl	**5**			**24**	A	68
14		CH_2-C_6H_4-OMe	**15**				B	87
15	"	COCl	**5**			**6**	A	65
16		CH_2-C_6H_4-OMe	**15**				B	88
17		CH_2-C_6H_4-OMe	**25**	Bn-NH_2		**26**	B	76
18		CH_2-C_6H_4-OMe	**27**	Bn-NH_2		**28**	B	51

[a] Isolated yield. [b] Method A: To the carbamoyl chloride in CH_2Cl_2 was added the tertiary amine and NEt_3 at rt.The mixture was stirred for 12 h and then treated with a saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The crude product was purified by flash chromatography. [c] Method B: To the tertiary amine in CH_2Cl_2 was added, at −10 °C, BTC in one portion. The reaction mixture was stirred for 1 h at rt. The secondary amine then NEt_3 were added and the mixture was stirred for 15 h before workup as in method A.

secondary amines.[40] Our method was applied to the one-pot synthesis of unsymmetrical ureas from tertiary amines and compared with the reaction of carbamoyl chlorides with secondary amines (Scheme 4). Table 3 described the results obtained from both procedures: directly by reaction between a carbamoyl chloride and

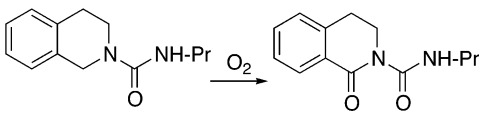
(39) Majer, P.; Randad, R. S. *J. Org. Chem.* **1994**, *59*, 1937−1938.

TABLE 4. Influence of Temperature, Amount of Substrate, and Solvent on the Formation of [^{11}C]2

entry	amine	amine (μmol)	solvent(s)	c (g·mL^{-1})	T (°C)	^{11}C-carbamoyl chloride	crude rcy[a] (%)	^{11}C-carbamoyl chloride[b] (%)
1	**13c**	154	toluene	0.13	20	**2**	59	81
2	**13c**	79	THF/CH_2Cl_2	0.1	−78	**2**	42	40
3	**13c**	59.3	THF/CH_2Cl_2	0.1	−78	**2**	45	18
4	**13c**	79	THF/CH_2Cl_2	0.1	−30	**2**	*c*	52
5	**13c**	79	THF/CH_2Cl_2	0.1	20	**2**	54	50
6	**13c**	39.5	THF/CH_2Cl_2	0.05	20	**2**	41	60
7	**13c**	7.9	THF/CH_2Cl_2	0.01	20	**2**	56	94
8	**13c**	3.95	THF/CH_2Cl_2	0.01	20	**2**	*c*	85
9	**13c**	7.9	CH_2Cl_2	0.01	20	**2**	(74)	100
10	**13d**	7	CH_2Cl_2	0.01	20	**2**	(76)	100
11	**15**	6.7	THF/CH_2Cl_2	0.1	−30	**5**	31 (28)	90
12	**15**	50.5	CH_2Cl_2	0.1	−30	**5**	(58)	100

[a] ±5−10%, decay corrected, calculated from the amount of radioactivity in the organic layer and the radioactivity of [^{11}C]phosgene used in the reaction. Each reaction was run at least twice. The isolated yields (HPLC) are given in parentheses. [b] Percentage (± 10%) of [^{11}C]carbamoyl chloride in the organic layer. [c] Not determined.

SCHEME 5



19 **29**

an amine (method A) or by a one-pot procedure involving the reaction of phosgene with a tertiary 4-methoxybenzylamine and subsequent addition of a primary or secondary amine (method B). The synthesis of tertiary amines bearing a 4-methoxybenzyl group was carried out by simple alkylation of the corresponding secondary amine with 4-methoxybenzyl chloride.[36]

Both methods gave the same yields of ureas starting with the tetrahydroisoquinoline derivatives (R = 4-methoxybenzyl or carbamoyl chloride, entries 1−8). As pointed out previously, tetrahydroisoquinoline carbamoyl chloride **2** was generated quantitatively from **13c** and triphosgene using method B. Piperazine-based ureas were obtained in good to excellent yields from method B. This method is particularly advantageous in this case, the carbamoyl chloride being unstable (entries 9−16). The lower yields obtained for these ureas derived from piperazine using method A were due to partial hydrolysis of carbamoyl chloride **5** prior its reaction with amines. The synthetic utility of method B was further exemplified in two more cases with nipecotate **25** and pipecolate **27** (entries 17 and 18). Method B appears a good alternative to other methods[41] for the preparation of unsymmetrical tri- or tetrasubstituted ureas. Some of these ureas were later used as reference compounds in radiolabeled compounds.

A point worth noticing is the instability of urea **19** (entries 1 and 2): after purification, this compound was oxidized rapidly (few days) upon standing in an open flask to the isoquinolinone **29** (Scheme 5). Such a reactivity toward molecular oxygen seems dependent on the degree of substitution of the urea. No benzylic oxidation was observed with urea **7**, and traces of α-oxo urea were observed with tetrahydroisoquinoline **20** after two months. To our knowledge, such an oxidation promoted by molecular oxygen on *N*-acyltetrahydroisoquinolines[42] has never been described on urea derivatives.

Overall, the debenzylation, especially the cleavage of electron-enriched benzyl groups, should be preferred over the demethylation in order to generate a carbamoyl chloride without urea production when utilizing a tertiary amine in the presence of phosgene (or BTC). This efficient and rapid method appeared tailor-made for the synthesis of ^{11}C-carbamoyl chlorides and was thus validated by the preparation and characterization of a few ^{11}C carbamoyl chlorides, ^{11}C ureas, one ^{11}C carbamate, and one ^{11}C amide.

Synthesis and Characterization of Two ^{11}C-Carbamoyl Chlorides. As model compounds, the [^{11}C]-carbamoyl chlorides **2** and **5** were synthesized via [^{11}C]-phosgene-promoted debenzylation of tertiary amines **13c** and **15**. [^{11}C]Phosgene was prepared from [^{11}C]methane according to a described procedure.[14] The reaction of [^{11}C]-phosgene with *N*-benzyltetrahydroisoquinoline **13b** was first studied under different conditions of temperature (−10, 20 °C), solvent (toluene, dichloromethane/THF), and amount of substrate (up to 10 mg). Radio-TLC analysis only showed the formation of traces of the expected [^{11}C]carbamoyl chloride **2** in a mixture of unidentified products.

[^{11}C]Phosgene-mediated debenzylation of 4-methoxybenzylamine **13c**, 2,4-dimethoxybenzylamine **13d**, and piperazine **15** were then studied. The results are presented in Table 4. When [^{11}C]phosgene was allowed to react with amine **13c** in a 1/1 mixture of toluene/dichloromethane (Table 4, entry 1), more than 80% of [^{11}C]carbamoyl chloride **2** were present in the crude product. No trace of the corresponding [^{11}C]urea **3** or the salt [^{11}C]**14c** was detected. Due to the efficiency of THF to trap [^{11}C]phosgene, and of dichloromethane to carry out the debenzylation, a 1/1 mixture of these solvents was then used. In this reaction medium, 50% of the total radioactivity was again recovered in the organic layer. The ratio of the expected [^{11}C]carbamoyl chloride **2** increased with the temperature until an optimum value at −30 °C (30% at −78 °C, about 50% at −30 and 20 °C) was reached. Comparison of entries 5−8 (Table 4) showed that the lower the amine concentration was (entry 7), the

(40) Huang, K.-T.; Sun, C.-*M. Biorg. Med. Chem. Lett.* **2001**, *11*, 271−273.

(41) See, i.e.: (a) Katritzky, A. R., Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155−4158. (b) Lamothe, M.; Perez, M.; Colovray-Gotteland, V.; Halazy, S. *Synlett.* **1996**, 507−508.

(42) (a) Ochiai, M.; Kajishima, D.; Sueda, T. *Tetrahedron Lett.* **1999**, *40*, 5541−5544. (b) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 2671−2676.

TABLE 5. Reactions of [^{11}C]Carbamoyl Chlorides 2 or 5 with Amines or with an Alcoholate

entry[a]	^{11}C-substrate[b]	reagent	mmol	^{11}C-product	crude rcy[c] (%)	^{11}C-product[d] (%)
1	**2**	Et_2NH	1	**7**	70	73
2	**2**	*n*-$PrNH_2$	0.85	**19**	57	77
3	**2**	**1**	0.56	**3**	nd	64
4	**2**	aniline	2.1	**21**	75	0
5	**2**	EtONa	0.15	**30**	94	74
6	**5**	Et_2NH	1	**23**	45	83
7	**5**	*n*$PrNH_2$	1.27	**22**	38	96
8	**5**	**4**	0.43	**6**	74	79
9	**5**	**1**	0.56	**24**	79	75

[a] Each reaction was carried out at least twice. [b] In CH_2Cl_2. [c] Decay corrected, ± 10%, from [^{11}C]phosgene. [d] Percentage of the expected ^{11}C-product in the crude mixture (from radio-TLC).

TABLE 6. Reaction of [^{11}C]-Labeled Carbamoyl Chloride 2 with Organometallics

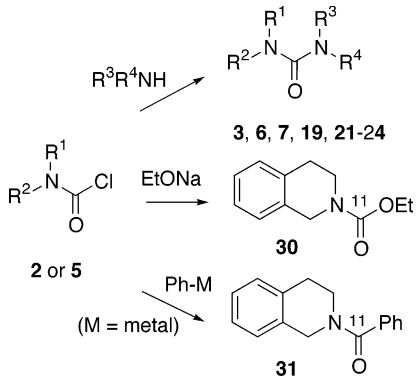
entry	amine (μmol)	solvent[a] (v/v/v)	reagent[b]	μmol	catalyst[c]	*T* (°C)	crude rcy[d] (%)	[^{11}C]**31**[e] (%)	[^{11}C]**2**[e] (%)
1	39.5	PhMe/THF/CH_2Cl_2 (5/1/1)	PhMgBr	70		20		0	57
2	39.5	PhMe/THF/CH_2Cl_2 (5/2/1)	PhMgBr	210		20		0	67
3	592	PhMe/THF/CH_2Cl_2 (5/3/1)	PhMgBr	105	$NiCl_2(PPh_3)_2$	20		0	66
4	79	THF/CH_2Cl_2 (3/2)	PhMgBr	70		−30	51	42	21
5	7	THF	PhMgBr	140		20	66	51	34
6	7.9	THF/CH_2Cl_2 (1/1)	PhMgBr	140	$NiCl_2(PPh_3)_2$	−30		44	18
7	39.5	THF/CH_2Cl_2 (1/1)	PhMgBr	140	$NiCl_2(PPh_3)_2$	−30		50	10
8	79	THF/CH_2Cl_2 (3/2)	PhMgBr	70	$NiCl_2(PPh_3)_2$	−30	24	55	13
9	3.9	THF/CH_2Cl_2 (1/1)	PhMgBr	140	$NiCl_2(PPh_3)_2$	−30	56	63	36
10	7	THF	$Ph_2CuMgBr{\cdot}BrMgCN$	56		−30	52	54	43

[a] Solvent or mixture of solvents used for the preparation of [^{11}C]**2**. [b] After addition of the reagent, and eventually the catalyst, the mixture was allowed to react for 5 min before addition of a saturated ammonium chloride solution and extraction with dichloromethane. [c] 2 mg (3.06 μmol). [d] From [^{11}C]**2**, decay corrected to EOB. [e] Ratio of [^{11}C]**31** or [^{11}C]**2** in the organic layer (from radioTLC).

higher the ratio of [^{11}C]carbamoyl chloride **2** was. Finally, when [^{11}C]phosgene was trapped in dichloromethane and the debenzylation carried out in the same solvent, the [^{11}C]carbamoyl chloride **2** was isolated in 74% radiochemical yield [decay corrected to the end of bombardment (EOB), 16 min total synthesis time]. Under similar conditions, the debenzylation of the 2,4-dimethoxybenzyl tetrahydroisoquinoline **13d** led to [^{11}C]carbamoyl chloride **2** in 76% isolated radiochemical yield (decay corrected to EOB, 16 min total synthesis time). Whereas the presence of two donor groups on the aromatic ring improved significantly the yields in stable isotope chemistry, no difference was noticed here. This could be explained by the large excess of tertiary amine (>7 μmol, entries 9 or 10) compared to the sub-micromolar amount of [^{11}C]phosgene. Only the ^{11}C-labeled carbamoyl chloride **5** was formed in the reaction of [^{11}C]phosgene with piperazine **15**. The purities (> 96%) of the ^{11}C-labeled carbamoyl chlorides **2** and **5** allowed their use, in further reactions, without any purification. Due to the low amounts of radioactivity used, no measurement of specific radioactivity was attempted.

Preliminary identifications of the [^{11}C]carbamoyl chlorides **2** and **5** were performed using LC and radio-TLC with co-injection of non-radioactive compounds. The unambiguous assigment of the ^{11}C-carbamoyl chlorides was deduced from the subsequent synthesis of [^{11}C]-derivatives (Scheme 6). In particular, [^{11}C]ureas **7** and **19** were formed by addition of the [^{11}C]carbamoyl chloride **2** to the corresponding amines in dichloromethane. The urea was shown only contaminated by the unreacted labeled starting material. Table 5 summarizes the main results. Under the conditions used, no reaction was observed with the non-nucleophilic aniline (Table 5, entry 4). However, a rapid reaction of [^{11}C]carbamoyl chloride

SCHEME 6



2 occurred with sodium ethanolate (Table 5, entry 5), and more than 94% of the carbamate **30** was formed in the crude reaction mixture. When [^{11}C]carbamoyl chloride **5** was allowed to react with amines for 5 min, more than 75% of ^{11}C-ureas **6** and **22**−**24** were present in the crude product, the remaining 25% being again the unreacted starting material.

Finally, [^{11}C]carbamoyl chloride **2** was treated with an organometallic under the conditions described in Table 6. A survey of the data shows the role of the solvent in the reaction of [^{11}C]-labeled carbamoyl chloride **2** with phenylmagnesium bromide at 20 °C. No [^{11}C]-labeled amide **31** was formed when toluene was used as the cosolvent whatever the reaction conditions: presence of the absence of catalyst (entries 1−3), high loading of amine (entry 3) or reagent (entry 2). Heating the mixture under reflux for 5 min did not transform the [^{11}C]-carbamoyl chloride **2** into the expected amide [^{11}C]**31**. When the reaction was performed in THF or THF/CH_2Cl_2, at −30 °C or at 20 °C for 5 min (Table 6, entries 4

and 5), formation of the [^{11}C]amide **31** was observed with some unreacted starting material and unidentified labeled compounds. A relative improvment in the yield of the [^{11}C]amide **31** was obtained using a small amount of amine and addition of $NiCl_2(PPh_3)_2$ (3 μmol) to the Grignard reagent at −30 °C. However, in no case was the reaction complete (Table 6, entries 6−10). Attempts to catalyze the reaction using methyldiphenylphosphine failed. Finally, the cyanocuprate $Ph_2CuMgBr{\cdot}BrMgCN$ was found to give the best results, the reaction mixture being easy to purify by HPLC (Table 6, entry 10), more than 97% of the radioactivity being recovered either as the target compound or the starting material.

Conclusion

In this paper, we have presented a versatile and efficient one-pot synthesis of carbamoyl chlorides. The key step, which was known as a side reaction until recently, was the phosgene (or triphosgene, its safe substitute) induced dealkylation of benzyl-substituted tertiary amines. An attractive feature of this methodology is that no symmetrical ureas are generated in the reaction. Moreover, it provides a useful strategy for the one-pot synthesis of unsymmetrical ureas and is particularly valuable when carbamoyl chlorides are unstable. In addition, electron-enriched benzyl substituents on the amine proved to be superior to benzyl or alkyl group. They allow the preparation of carbamoyl chlorides derived from less reactive tertiary benzyl anilines. In addition, we have demonstrated the utility of this phosgene-mediated debenzylation of tertiary amines by preparing two ^{11}C-labeled carbamoyl chlorides in 58−75% yields (decay corrected, 20 min total synthesis time from [^{11}C]CH_4). They were characterized by their transformations into ^{11}C-labeled unsymmetrical acyclic ureas or carbamate and one ^{11}C-amide. The simplicity and efficiency of the method has a great potential both in organic synthesis and in any type of carbonyl-labeling chemistry when phosgene must be used in a limited amount. The paramethoxybenzyl group, already known as a protecting group for secondary amines, can be considered as a direct group relay for the synthesis of carbamoyl chlorides and subsequently of unsymmetrical ureas, as well as carbamates and amides.[6]

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Supporting Information Available: Experimental procedures and full charaterization for new compounds are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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