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Phenyloxycarbonyl (Phoc) Carbamate: Chemioselective Reactivity and Tetra-*n*-butylammonium Fluoride Deprotection Study

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Cite This: *ACS Omega* 2022, 7, 44861−44868

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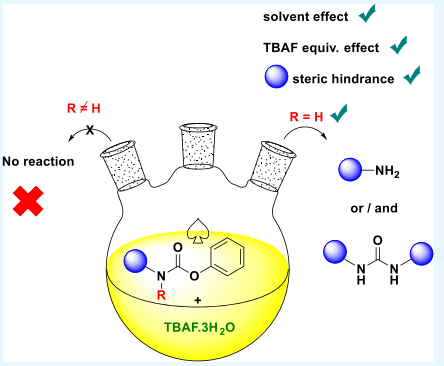
ABSTRACT: We present the results of the chemoselective reactivity of phenylcarbamates. Phenylcarbamates of primary amines are reactive to form urea, and phenylcarbamates of secondary amines can be used as tags due to the existence of rotamers. Moreover, deprotection attempts to to recover the primary amines in use of a catalytic amount of TBAF show the possibility of obtaining the symmetrical urea from the corresponding phenylcarbamate. We have begun the study of the transformation of Phoc carbamates into the corresponding free amines by TBAF. We present here our most significant results concerning the sensitivity of this reaction in terms of the solvent and substrate.



INTRODUCTION

Carbamates[1] and phenylcarbamates are widely described in the literature, primarily *para*-nitrophenyl carbamates. Although they have a strong group leaving group, phenylcarbamates are very stable over time and thus, they allow the preparation of synthon on a large scale. The use of phenyloxycarbonyl (Phoc) as an amine protecting group for peptide synthesis has been studied, but Phoc was rapidly displaced by Boc and Fmoc because of intramolecular cyclization reactions in peptides.[2] A revival of phenyloxycarbamates occurred for the preparation of oxazolidinone, urea, and polyurea[3] and more recently for the synthesis of the peptide bond via amide formation without a coupling agent.[4] In our group, we work on peptides and/or peptidomimetics to inhibit protein−protein interactions, and this approach would be very useful in synthesis.

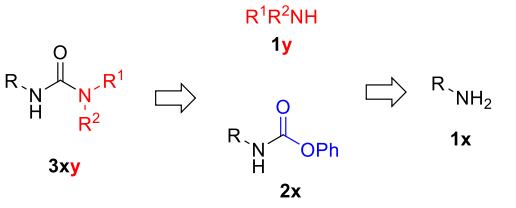
The use of urea in the synthesis of biologically active compounds[5] or for the preparation of organic materials is experiencing a revival.[6] In therapy, the urea motif is likened to an amide and it can be used as an amide bioisostere or in the case of peptide cyclization. An important development is in the formation of cyclic peptides[7] and polyurea as a peptidomimetic,[8] where structuring of these polyureas is perfectly defined.[9]

The *para*-nitrophenyloxycarbonyl group is more reactive than the simple phenyloxycarbonyl group, and the yellow color of the *para*-nitrophenol makes it possible to gauge the transformation of the *para*-nitrophenyloxycarbonyl group. However, phenylcarbamates have the advantage of being stable in an organic acid medium and in an aqueous medium (except in the presence of hydroxide ions),[10,11] allowing isolation and purification by flash chromatography. As part of our work on the synthesis of bioactive molecules containing the urea motif[12] and the special reactivity of these ureas,[13] we scope the limitation of the Phoc strategy for preparation of valuable synthons.[14]

RESULTS AND DISCUSSION

To facilitate the understanding of the nomenclature of urea formation, we have systematically assigned the name **3xy** (Scheme 1). Phoc carbamate **2x** from amine **1x** is coupled to amine **1y** to form the asymmetric **3xy** urea. Due to the symmetry of the urea moiety, compound **3xy** is identical to compound **3yx**. The symmetrical ureas are thus systematically noted **3xx**.

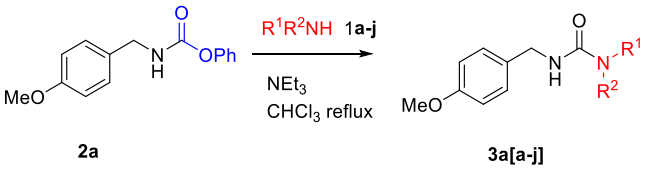
Scheme 1. Retrosynthesis and Nomenclature of Ureas 3



Received: August 4, 2022
Accepted: October 12, 2022
Published: November 28, 2022

https://doi.org/10.1021/acsomega.2c04979
ACS Omega 2022, 7, 44861−44868

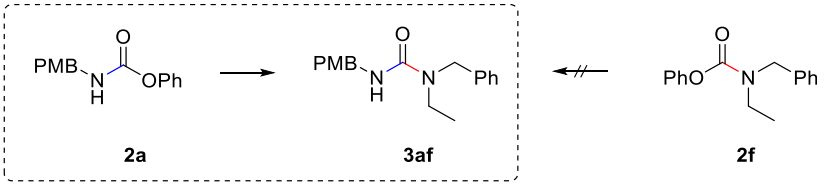
Table 1. Substituent Effect for Phoc Coupling with Amine for the Synthesis of Urea



2a 3a[a-j]

entry	R^1R^2NH 1a–j	R^1	R^2	urea	yield
1	PMB–NH_2 **1a**	PMB	H	**3aa**	89%
2	*n*-pentyl–NH_2 **1b**	*n*-pentyl	H	**3ab**	88%
3	*t*Bu–NH_2 **1c**	*t*Bu	H	**3ac**	85%
4	Ph–NH_2 **1d**	Ph	H		no reaction[a]
5	Bn–NH_2 **1e**	Bn	H	**3ae**	90%
6	Bn(Et)NH **1f**	Bn	Et	**3af**	84%
7	4-NH_2–Bn–NH_2 **1g**	4-NH_2–Bn	H	**3ag**	65%
8	EtO_2C–CH_2CH_2–NH_2 **1h**	$CH_2CH_2CO_2Et$	H	**3ah**	80%
9	*t*BuO_2C–CH_2–NH_2 **1i**	CH_2CO_2*t*Bu	H	**3ai**	85%
10	HO_2C–CH_2–NH_2 **1j**	CH_2CO_2H	H	**3aj**	72%

[a]**2a** was fully recovered.



2a 3af 2f

Figure 1. Urea **3af** synthetic strategy from Phoc carbamate.

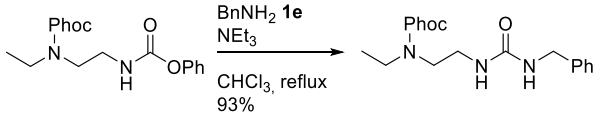
In order to easily follow the reaction by UV spectroscopy, we used the Phoc of carbamate *para*-methoxy-benzylamine **2a**. We chose to study this reaction in chloroform in the presence of triethylamine as a base. In the absence of triethylamine or refluxing chloroform, no urea is formed. The nucleophilicity of the amine is essential, and aniline **1d** does not lead to the desired urea (Table 1, entry 4), but no degradation of carbamate **2a** was observed. Non-reactivity of aromatic primary amines in our conditions is confirmed by the chemoselective reactivity of 4-aminobenzylamine: only the addition of the aliphatic primary amine on carbamate **2a** is effective to afford urea **3ag**; thereby, we can use aromatic amines without protection. Amino acids, as free acids or ester derivatives, react very well (Table 1, entries 8–10), and no trace of hydantoin was detected.

Obtaining urea **3af** by creating the C–N bond starting from carbamate **2f** is not possible (Figure 1), even under conditions in high concentration of a base and at a higher temperature. Carbamate **2f** is integrally recovered, demonstrating the stability of *N*,*N*-disubstituted phenylcarbamates under hard conditions.

This chemoselective reactivity of Phoc carbamate was studied from *N*-ethyl-1,2-diamine (Scheme 2). Protecting both amine functions is performed in the classic conditions of the laboratory to yield bis(carbamate) **2k**. Selective transformation of the NH-Phoc moiety is observed: only dissymmetric urea **3ke** is formed in our reaction conditions after mixing bis(carbamate) **2k** and excess of benzylamine **1e**.

An important point is the existence of rotamers for carbamates derived from secondary amines. ^1H and ^{13}C NMR spectra made at different temperatures show coalescence of the signal (Figure 2). Conformers can track reactivity or stability of the phenylcarbamate from secondary amines by simple NMR analysis. For example, ^1H NMR spectra of **2k** and **3ke** (see the Supporting Information) indicate the existence of rotamers, confirming the presence of a Phoc derived from a secondary amine.

Scheme 2. Chemioselective Reactivity of Bis-Phoc Carbamate 1k



2k 3ke

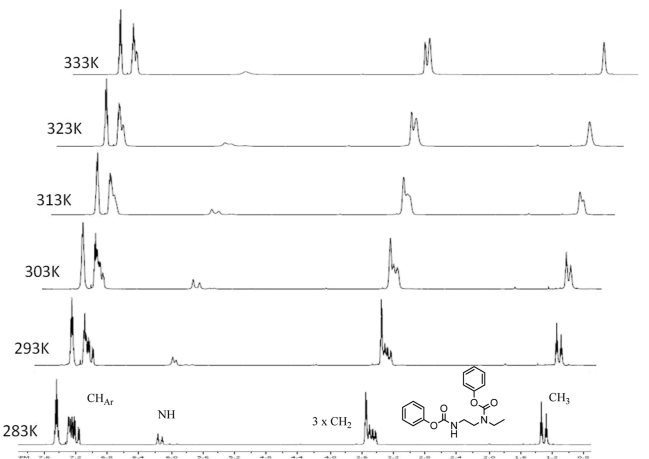


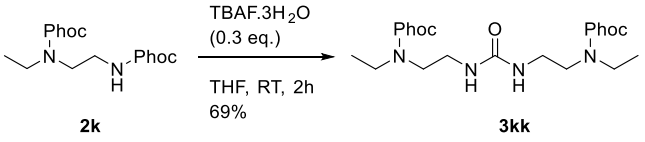
Figure 2. Rotamers of **2k** by ^1H NMR coalescence experimentation ($CDCl_3$).

https://doi.org/10.1021/acsomega.2c04979
ACS Omega 2022, 7, 44861–44868

The phenylcarbamate is very stable in an acidic aqueous medium and relatively stable in a dilute basic aqueous medium, so we can perform aqueous work-up using a saturated solution of $NaHCO_3$ or KOH (1 M). We use this Phoc group very widely in our research. However, the deprotection is carried out in a strong basic medium by the use of hydroxide anions (or a strong basic resin), so this deprotection is not compatible with a large number of chemical functions. We also investigated the reactivity of Phoc at room temperature using TBAF. We were intrigued by the results of Jacquemard concerning the deprotection of the Phoc group with TBAF.[15]

The mechanism of the basic hydrolysis of Phoc carbamates differs according to the number of substituents on the nitrogen atom. In particular, Phoc carbamates from primary amines react via an E1cb-type mechanism by in situ formation of an isocyanate intermediate.[16] For the *N*,*N*-disubstituted carbamate phenyl esters (i.e., RR′*N*-Phoc), the reaction conditions are more drastic via a $B_{Ac}2$ mechanism.[11] In our research work, we were surprised to obtain mainly symmetrical urea **3kk** (Scheme 3) and not the free amine under the reaction

Scheme 3. Unexpected Synthesis of Symmetric Urea 3kk Mediated by TBAF

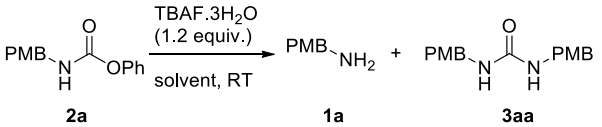


2k **3kk**

conditions of ref 15. Once again, only the Phoc group of the primary amine is involved in the reaction, which suggests the need for a labile hydrogen on the nitrogen atom for the Phoc group to react.

Therefore, we have begun the study of the reactivity of Phoc carbamates with TBAF. Using carbamate **2a** as a reference, we looked for the effect of the solvent (Table 2). In THF, an

Table 2. Solvent Effect on Phoc 2a Deprotection Mediated by TBAF



2a **1a** **3aa**

no	solvent	ratio **2a**:**1a**:**3aa**[a] (30 mn)
1	THF	0:42:58
2	$CHCl_3$	86:0:14[b]
3	MeCN	0:0:100
4	DMSO	0:0:100[c]
5	MeOH	no reaction

[a]^{1}H NMR in the crude mixture. [b]Complete formation of **3aa** in 72 h. [c]Complex mixture of polyurea.

almost equimolar mixture of amine **1a** and urea **3aa** is rapidly obtained (entry 1, Table 2). Theoretically, if only amine **1a** and urea **3aa** could be formed by consumption of Phoc carbamate **2a**, the maximum ratio should be **1a**:**3aa** close to 33:67, which is what we get. The reaction is much slower in chloroform with an exclusive formation of urea **3aa** after 72 h. The use of the more polar solvent MeCN leads to the exclusive and fast formation of urea **3aa**. In DMSO (entry 4, Table 2), we note the formation of urea **3aa** without amine **1a**, but other signs indicate the presence of undetermined structures. Although NMR monitoring shows a modification of the chemical shifts of compound **2a** (see the Supporting Information), the reaction carried out in methanol leads to no reaction and contains only reagent **2a**.

Using THF as the reference solvent, we investigated the effect of the TBAF amount on the amine/urea ratio (Table 3).

Table 3. TBAF Equivalent Effect on Phoc 2a Deprotection[a]

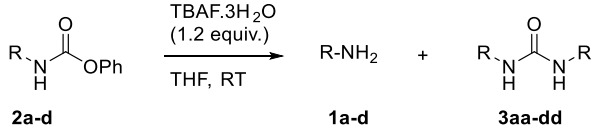
no	TBAF (equiv)	time	ratio **1a**:**3aa**[b]
1	0.3	20 h	0:100[c]
2	0.6	2 h	17:83
3	1.2	30 min	42:58
4	2.4	10 min	19:81[d]
5	5.0	5 min	n.d.[e]

[a]Reaction performed in THF. [b]^{1}H NMR in the crude mixture. [c]88% yield of purified **3aa**. [d]**1a** and **3aa** are minor products. [e]Complex mixture of **3aa** and polyurea (see the Supporting Information).

It should be noted that the reaction is effective with less than 1 equiv (relative to Phoc carbamate **2a**). However, lowering the amount of TBAF promotes the formation of urea **3aa**, which is consistent with the formation reaction of urea **3kk** (Scheme 3). Unfortunately, an increase in the amount of TBAF does not make it possible to increase the proportion of amine **1a** but makes the reaction medium complex, likely by the formation of novel polyurea molecules.

By fixing the optimum amount of TBAF for obtaining the amine from Phoc **2a**, we studied the effect of the *N*-substituted phenylcarbamate with aliphatic, aromatic, and hindered groups (Table 4). The Phoc compounds and symmetric ureas are prepared according to the usual laboratory method (Scheme 3); **3dd** urea was purchased.

Table 4. Substituent Effect on Phoc Deprotection Mediated by TBAF



2a-d **1a-d** **3aa-dd**

entry	Phoc carbamate	R	ratio amine/urea[a]
1	**2a**	PMB	**1a**:**3aa** 42:58
2	**2b**	*n*-pentyl	**1b**:**3bb** 0:100[b]
3	**2c**	*t*Bu	**1c**:**3cc** 94:4
4	**2d**	Ph	**1d**:**3dd** 100:0

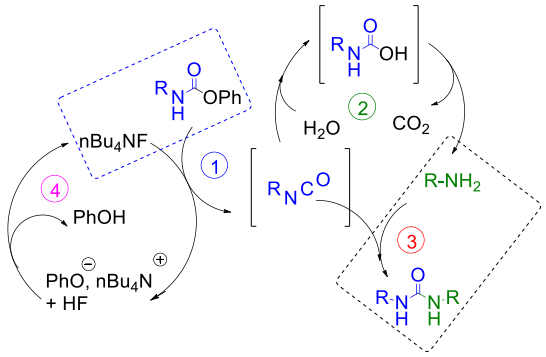
[a]^{1}H NMR in the crude mixture. [b]89% yield of purified **3bb**.

From carbamate **2d**, only aniline **1d** is formed. Hydrolysis of the aromatic amine Phoc by TBAF would selectively yield the corresponding amine.[17] Since the aromatic amine is very little nucleophilic, the hydrolysis of the isocyanate is then faster than the addition of the amine to give the urea (Scheme 4). For the aliphatic amines, the size of the substituent modulates the proportion of the corresponding amine and urea. The very bulky, *tert*-butyl group favors the formation of *tert*-butylamine **1c** from carbamate **2c**. Conversely, 1,3-bis(pentylurea) **3bb** is selectively obtained from Phoc carbamate **2b**.

The intermediate steric size of the PMB group gives an almost equimolar mixture of amine **1a** and the corresponding urea **3aa**. For the aliphatic amines, the size of the substituent

https://doi.org/10.1021/acsomega.2c04979
ACS Omega 2022, 7, 44861−44868

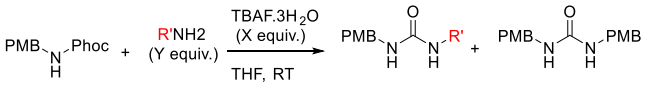
Scheme 4. Proposed Mechanism of Phoc Carbamate Hydrolysis Mediated by TBAF



modulates the proportion of the corresponding amine and urea. Interestingly, carbamate **2f** (Scheme 1) does not react under these conditions to afford free amine or the corresponding urea, supporting the idea that the presence of a labile proton is obligatory to initiate the reaction.

With all the data in hand, we can propose a mechanism for the reaction of TBAF with phenylcarbamate. This reactivity is consistent with the mechanisms proposed in the literature for the basic hydrolysis via passage through an isocyanate intermediate resulting from the deprotonation of the ionizable NH-Phoc (step 1, Scheme 4).[16] The isocyanate intermediate is hydrolyzed to amine by the water molecules present in TBAF (step 2, Scheme 4). Depending on the nature of the amine formed, this amine can trap the isocyanate intermediate to yield the corresponding urea (step 3, Scheme 4), which is corroborated by the results in Table 5. Moreover, by using a

Table 5. Amine Trapping Effect on Phoc Carbamate 2a Deprotection Mediated by TBAF



2a 3a[a-c] 3aa

entry	amine	R′	*Y* (equiv)	*X* (equiv)	urea ratio[a]
1	**1c**	*t*Bu	20	1.2	**3ac**:**3aa** 100:0[b]
2	**1c**	*t*Bu	1.0	1.2	**3ac**:**3aa** 60:40
3	**1c**	*t*Bu	1.0	0.25	**3ac**:**3aa** 86:14
4	**1b**	*n*-pentyl	1.0	1.2	**3ab**:**3aa** 100:0[c]
5	**1a**	PMB	1.0	1.2	**3aa** 100[d]

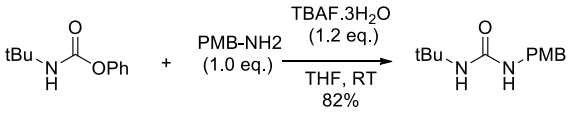
[a]^{1}H NMR in the crude mixture. [b]93% yield of purified product **3ac**. [c]85% yield of purified product **3ab**. [d]92% yield of purified product **3aa**.

catalytic amount of TBAF, the hydrolysis of the Phoc group is relatively slowed down, allowing the amine to trap the isocyanate formed in situ, even if this amine is not very nucleophilic for steric reasons (i.e., *tert*-butylamine).

It is unclear whether TBAF is reformed or whether the phenolate anion serves as the basis for step 1. We have already described the activation of ureas by TBAF,[13a] and in this case, no other base is present. Unfortunately, ^{19}F NMR reaction monitoring was inconclusive.

This mechanistic hypothesis is supported by trapping experiments of the isocyanate intermediate (Table 5). In the presence of a large excess of *tert*-butylamine **1a**, dissymmetric urea **3ac** is quantitatively formed (entry 2, Table 5). With a single equivalent, a majority of dissymmetric urea **3ac** is formed with respect to symmetrical urea **3aa** (entry 2, Table 5). By comparison, dissymmetric urea **3ab** is the only product obtained under the same reaction conditions using *n*-pentylamine, a less sterically hindered amine (entry 4, Table 5). The proportion of dissymetric urea **3ac** can be increased with a single equivalent of *tert*-butylamine **1c** using a catalytic amount of TBAF (entry 1, Table 5): in this case, the formation of amine **1a** is slowed, allowing time for the *tert*-butylamine to react despite a nucleophilic character diminished by steric hindrance. The use of a catalytic amount of TBAF (entry 3, Table 5) allows a relative increase in dissymmetrical urea **3ac**. One justification is the presence of a lower quantity of amine **1a** resulting from the hydrolysis of Phoc carbamate **2a**: in the first catalytic round, a maximum of 0.25 equiv of amine **1a** would be formed in the presence of 1.0 equiv of amine **1c**. Even if amine **1c** is less nucleophilic than **1a**, its presence in a major proportion allows the attack of the isocyanate resulting from **2a** before competing with amine **1a**. With 1.2 equiv of TBAF, the proportion of amine **1a** increases more rapidly; hence, there is a higher final proportion of dissymmetrical urea **3aa** (entry 2, Table 5). By reversing the place of the substituents (Scheme 5), only **3ac** urea is obtained with 1.2 equiv of TBAF.

Scheme 5. Amine Trapping Effect on Phoc Carbamte 2c Deprotection Mediated by TBAF



2c 3ac

The steric factor is evidenced by the exclusive formation of the dissymmetric urea **3ac** from Phoc carbamate **2c** in the presence of an equivalent of *p*-methoxybenzylamine **1a** and 1.2 equiv of TBAF (Scheme 5). Under these conditions, the symmetric urea **3cc** is not detected. Since *p*-methoxybenzylamine is less sterically bulky, the addition is much more effective with carbamate **2c** than that of *tert*-butylamine with **1a** (entry 2, Table 4).

CONCLUSIONS

In summary, we showed that the phenylcarbamate serves as both a protective group for amines and a chemoselective group to discriminate phenyl carbamates of primary or secondary amines. Dissymmetric ureas were obtained with very good yields, with total selectivity for aliphatic versus aromatic amines. We can perform the formation of symmetrical urea under mild conditions using a catalytic amount of TBAF. This kind of tool could have a major role in peptidic and pseudopeptide chemistry. We continue our research in this direction for the preparation of dissymmetric ureas.

EXPERIMENTAL SECTION

General Information and Materials. *General Consideration.* All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. Melting points were uncorrected. Thin-layer chromatograms were run on glass plates coated with silica gel G for thin-layer chromatography (TLC) using the solvent system EtOAc/cyclohexane. Compounds were

https://doi.org/10.1021/acsomega.2c04979
ACS Omega 2022, 7, 44861−44868

purified by column chromatography using silica gel (40−63 mesh) with EtOAc/cyclohexane (of a specific proportion as required) as an eluent. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) were recorded using $CDCl_3$, DMSO-d_6, or MeOD as a solvent. Chemical shifts (δ) are reported in parts per million (ppm), with the internal reference (0.05 to 1%) tetramethylsilane. Coupling constants (J) are reported in Hz: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br). High-resolution mass spectrometry (HRMS) was performed on a Q-TOF Waters spectrometer and an electrospray ionization (ESI) ion source. IR spectra were recorded on a Jasco FT-IR spectrometer. Data for previously reported compounds (cited) matched well with our observed data.

Preparation of Phenyl Carbamate (General Procedure). For starting materials listed in Table 1, the following protocol was used: phenyl chloroformate (5.5 mmol, 1.1 equiv) in one portion was added to a magnetically stirred solution of amine (5.0 mmol, 1.0 equiv) in dry THF (20.0 mL) at room temperature under an Ar atmosphere. The reaction mixture was stirred at room temperature until complete consumption of starting materials monitored by TLC and then diluted with 1 N NaOH aqueous solution. The resulting mixture was extracted twice with dichloromethane, and the combined organic extracts were washed with brine and dried with $MgSO_4$. Then, it was evaporated to dryness, and the residue was purified by flash column chromatography to give phenyl carbamate.

*Phenyl 4-Methoxybenzylcarbamate (**2a**).* Yield: 1.2 g (94%). White solid. R_f 0.32 (15% EtOAc in cyclohexane); mp: 88 °C; FTIR (neat) 3292, 3077, 1699, 15432, 1515, 1483, 1248 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (m, 2H), 7.30 (m, 2H), 7.24−7.15 (m, 3H), 6.92 (d, J = 8.1 Hz, 2H), 5.33 (br.s, 1H), 4.41 (d, J = 5.8 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 154.6, 151.1, 130.1, 129.3 (× 2), 129.1, 125.3, 121.6, 114.2, 55.3, 44.8. HRMS (ESI): calcd for $C_{15}H_{15}NO_3Na$ [M + Na]$^+$, 280.0950; found, 280.0960.

*Phenyl n-Pentylcarbamate (**2b**).* Yield: 890 mg (86%). White solid. R_f 0.38 (15% EtOAc in cyclohexane). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.70 (t, J = 5.1 Hz, 1H), 7.37 (m, 2H), 7.19 (m, 1H), 7.09 (m, 2H), 3.05 (td, J = 6.5, 5.1 Hz, 2H), 1.48 (m, 2H), 1.38−1.22 (m, 4H), 0.89 (t, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.8, 151.6, 129.6, 125.2, 122.2, 40.9, 29.3, 28.9, 22.3, 14.3. Chemical and spectroscopic data are identical to those from a previous report.[18]

*Phenyl tert-Butylcarbamate (**2c**).* Yield: 820 mg (85%). White solid. R_f 0.32 (15% EtOAc in cyclohexane). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.53 (brs, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.19 (dd, J = 8.4,7.2 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 153.7, 151.5, 129.6, 125.1, 122.3, 50.2, 29.9. Chemical and spectroscopic data are identical to those from a previous report.[19]

*Phenyl Phenylcarbamate (**2d**).* Yield: 930 mg (87%). White solid. R_f 0.3 (10% EtOAc in cyclohexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.22 (bs, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 8.2 Hz, 2H), 7.36−7.20 (m, 5H), 7.05 (t, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 152.2, 151.0, 139.1, 129.9, 129.3, 125.9, 123.4, 122.4, 118.9. Chemical and spectroscopic data are identical to those from a previous report.[20]

*Phenyl Benzyl(ethyl)carbamate (**2f**).* Yield: 1.21 g (94%). Yellow oil. R_f 0.40 (10% EtOAc in cyclohexanes). FTIR (neat) 3028, 2977, 2942, 1715, 1495, 1468, 1455, 1416, 1249, 1200 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4−7.2 (m, 7H), 7.2−7.0 (m, 3H), 4.56 and 4.49 (s, 2H), 3.33 (q, J = 7.2 Hz, 2H), 1.11 and 1.10 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 154.4, 129.4, 128.8, 128.2, 127.6, 127.4, 125.3, 121.9, 50.6, 50.5, 42.5, 41.9, 13.7, 13.0. HRMS (ESI): calcd for $C_{16}H_{17}NO_2Na$ [M + Na]$^+$, 278.1157; found, 278.1152.

*Phenyl Ethyl(2-((phenoxycarbonyl)amino)ethyl)-carbamate (**2k**).* Yield: 1.51 g (93%). Yellowish solid. R_f = 0.32 (30% EtOAc in cyclohexane). mp: 74−75 °C. FTIR (neat) 3316, 2965, 2941, 1741, 1694, 1538, 1493, 1474, 1424, 1280, 1250, 1210 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.5−7.3 (m, 4H), 7.3−7.0 (m, 2H), 5.72 and 5.48 (brs, 1H), 3.4−3.7 (m, 6H), 1.4−1.2 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.4, 155.1, 155.0, 154.4, 151.4, 151.1, 151.0, 129.3, 125.3, 125.2, 121.8, 121.7, 121.6, 46.8, 46.2, 43.1, 43.0, 40.0, 39.9, 14.0, 13.1. HRMS (ESI): calcd for $C_{18}H_{20}N_2NaO_4$ [M + Na]$^+$, 351.1321; found, 351.1335.

Preparation of Urea (Table 1). For experiments listed in Table 4, the following protocol was used: A mixture of phenyl carbamate (1.0 mmol, 1.0 equiv), NEt_3 (3.0 mmol), and selected amine (1.2 mmol, 1.2 equiv) in chloroform (10 mL) was refluxed for 48 h. The cooled reaction mixture was diluted with dichloromethane and extracted with 1 N NaOH aqueous solution. The combined organic phase was washed with 2 N HCl aqueous solution, dried, and evaporated to dryness. The residue was purified by flash column chromatography to afford pure urea.

*1,3-Bis-(4-methoxybenzyl)urea (**3aa**).* Yield: 270 mg (89%). White powder. mp: 177.7−178.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.17 (d, J = 8.2 Hz, 4H), 6.87 (d, J = 8.1 Hz, 4H), 6.28 (t, J = 5.7 Hz, 2H), 4.15 (d, J = 5.7 Hz, 4H), 3.73 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.5, 158.4, 133.3, 128.8, 114.1, 55.5, 42.9. Chemical and spectroscopic data are identical to those from a previous report.[21]

*1-(4-Methoxybenzyl)-3-pentylurea (**3ab**).* Yield: 220 mg (88%). White powder. mp: 112−114 °C. FTIR (neat) 3350, 3324, 3100, 2952, 2923, 1618, 1579, 1513, 1253, 1241, 1172, 1109, 1031, 811 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.16 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.14 (t, J = 5.8 Hz, 1H), 5.83 (t, J = 5.5 Hz, 1H), 4.11 (d, J = 5.8, 2H), 3.73 (s, 3H), 2.99 (q, J = 6.7 Hz, 2H), 1.42−1.15 (m, 6H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.4, 133.4, 128.8, 114.1, 55.5, 42.8, 39.7, 30.2, 22.3, 14.4. HRMS (ESI): calcd for $C_{14}H_{22}N_2O_2Na$ [M + Na]$^+$, 273.1570; found, 273.1579.

*1-(tert-Butyl)-3-(3-methoxybenzyl)urea (**3ac**).* Yield: 200 mg (85%). White powder. mp: 100−102 °C. FTIR (neat) 3356, 3318, 3100, 2961, 2917, 1631, 1564, 1512, 1260, 1250, 1173, 1037, 1031 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.15 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.97 (t, J = 5.8 Hz, 1H), 5.67 (s, 1H), 4.08 (d, J = 5.8, 2H), 3.73 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.5, 157.8, 133.3, 128.7, 114.1, 55.5, 49.5, 42.5, 29.8. HRMS (ESI): calcd for $C_{13}H_{20}N_2O_2Na$ [M + Na]$^+$, 259.1413; found, 259.1422.

*1-Benzyl-3-(4-methoxybenzyl)urea (**3ae**).* Yield: 245 mg (90%). White solid. R_f 0.38 (50% EtOAc in cyclohexane). mp: 126 °C. FTIR (neat) 3349, 3316, 2954, 1624, 1575, 1512, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.28 (m, 5H), 7.11 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 4.29

https://doi.org/10.1021/acsomega.2c04979
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(s, 2H), 4.23 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.0, 138.9, 130.9, 128.8, 128.7, 127.4, 127.3, 114.1, 55.3, 44.6, 44.2. Chemical and spectroscopic data are identical to those from a previous report.[22]

*1-Benzyl-1-ethyl-3-(4-methoxybenzyl)urea (**3af**).* Yield: 250 mg (84%). Yellow oil. R_f. 0.2 (30% EtOAc in cyclohexane). FTIR (neat) 3352, 3031, 2965, 2928, 1627, 1532, 1510, 1453, 1404, 1361, 1243 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4−7.3 (m, 5H), 7.18 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.78 (t, J = 5.4 Hz, 1H), 4.52 (s, 2H), 4.39 (d, J = 5.4 Hz, 2H), 3.81 (s, 3H), 3.36 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 157.9, 138.2, 131.8, 128.8, 128.7, 127.3, 127.1, 113.9, 55.3, 49.9, 44.4, 41.9, 13.4. HRMS ESI(−): calcd for $C_{18}H_{22}N_2O_2$ [M − H] 297.1603; found, 297.1609.

*1-(4-Aminobenzyl)-3-(4-methoxybenzyl)urea (**3ag**).* Yield: 186 mg (65%). Yellow solid. R_f. 0.6 (100% EtOAc). mp: 184 °C. FTIR (neat) 3462, 3336, 2957, 2877, 1609, 1597, 1585, 1564, 1514, 1472, 1303, 1285, 1247 cm^{-1}. ^{1}H NMR (400 MHz, MeOD) δ: 7.20 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.2 Hz, 2H), 4.20 (s, 2H), 4.26 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ: 159.6, 158.8, 146.2, 131.8, 129.2, 128.1, 127.9, 115.2, 113.5, 54.3, 43.2, 42.9. HRMS (ESI): calcd for $C_{16}H_{19}N_3O_2Na$ [M + Na]$^+$, 308.1375; found, 308.1381.

*Ethyl 3-(3-(4-Methoxybenzyl)ureido)propanoate (**3ah**).* Yield: 225 mg (80%). Brown solid. R_f. 0.12 (50% EtOAc in cyclohexanes). mp: 97−98 °C. FTIR (neat) 3325, 2924, 1724, 1714, 1611, 1577, 1512, 1439, 1334, 1301, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 4.30 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H, 3.81 (s, 3H), 3.79 (t, J = 4.6 Hz, 2H), 2.54 (t, J = 4.6 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 158.9, 158.0, 131.0, 128.8, 114.0, 60.7, 55.3, 44.1, 35.9, 34.8, 14.2. HRMS (ESI): calcd for $C_{14}H_{20}N_2O_4Na$ [M + Na]$^+$, 303.1321; found, 303.1324.

*tert-Butyl 2-(3-(4-Methoxybenzyl)ureido)acetate (**3ai**).* Yield: 250 mg (85%). White solid. R_f. 0.31 (50% EtOAc in cyclohexanes). mp: 95−96 °C. FTIR (neat) 3315, 3047, 2985, 2968, 1733, 1617, 1558, 1174, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 4.65 (br, 2H), 4.28 (s, 2H), 3.87 (s, 2H), 3.79 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 158.9, 158.0, 131.0, 128.8, 114.0, 82.0, 55.3, 44.0, 42.9, 28.0. HRMS (ESI): calcd for $C_{15}H_{22}N_2O_2Na$ [M + Na]$^+$, 317.1477; found, 317.1479.

*2-(3-(4-Methoxybenzyl)ureido)acetic Acid (**3aj**).* Yield: 172 mg (72%). White solid. R_f. 0.11 (100% AcOEt). mp: 180−182 °C. FTIR (neat) 3379, 3314, 2951, 1695, 1624, 1592, 1582, 1513, 1411, 1282, 1231 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.42 (brs, 1H), 7.17 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.55 (t, J = 5.8 Hz, 1H), 6.14 (t, J = 5.8 Hz, 1H), 4.13 (d, J = 5.8 Hz, 2H), 3.72 (s, 3H), 3.71 (d, J = 5.8 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.0, 158.5, 158.4, 133.1, 128.8, 114.0, 55.5, 42.8, 42.0. HRMS (ESI): calcd for $C_{11}H_{14}N_2O_4Na$ [M + Na]$^+$, 261.0851; found, 261.0853.

*Phenyl (2-(3-Benzylureido)ethyl)(ethyl)carbamate (**3ke**).* Yield: 318 mg (93%). Yellow oil. R_f. 0.30 (65% EtOAc in cyclohexanes). FTIR (neat) 3361, 3020, 2934, 1717, 1633, 1560, 1471, 1417, 1253, 1201, 1145 cm^{-1}. ^{1}H NMR (400 MHz, MeOD) δ: 7.2−7.4 (m, 7H), 7.12 (m, 2H), 4.31 (d, J = 11.8 Hz, 2H), 3.60−3.35 (m, 6H, CH_2), 1.27 and 1.19 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ: 159.6, 155.4, 154.0, 139.9, 139.8, 128.9, 128.1, 126.9, 126.6, 125.0, 121.6, 121.5, 47.1, 46.8, 43.4, 42.8, 42.7, 38.3, 38.0, 12.8, 11.9. HRMS (ESI): calcd for $C_{19}H_{23}N_3O_3Na$ [M + Na]$^+$, 364.1637; found, 364.1624.

*1,3-Dibutylurea (**3cc**).* Yield: 155 mg (90%). Colorless solid. R_f. 0.35 (50% EtOAc in cyclohexane). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.44 (s, 2H), 1.19 (s, 18H). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 157.5, 49.2, 29.8. Chemical and spectroscopic data are identical to those from a previous report.[23]

*Diphenyl ((Carbonylbis(azanediyl))bis(ethane-2,1-diyl))-bis(ethylcarbamate) (**3kk**).* A solution of carbamate **1k** (328 mg, 1.0 mmol) in dry THF (10 mL) was stirred at room temperature under argon. A freshly prepared 1 M solution of TBAF in THF (0.3 equiv) was added and stirred at room temperature until complete consumption of starting materials monitored by TLC; then water (20 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, dried, and evaporated to dryness. The residue was purified by flash column chromatography to afford pure urea **3kk**. Yield: 305 mg (69%). Brownish solid. R_f. 0.24 (50% EtOAc in cyclohexanes). mp: 122−123 °C. FTIR (neat): 3340, 3008, 2928, 1716, 1574, 1472, 1421, 1264, 1200, 1145, 1038, 955 cm^{-1}. ^{1}H NMR (400 MHz, MeOD) δ: 7.39 (m, 4H), 7.23 (m, 2H), 7.13 (m, 4H), 3.60−3.32 (m, 12H), 1.35−1.10 (m, 6H). ^{13}C NMR (100 MHz, MeOD) δ: 159.6, 155.3, 154.9, 152.4, 128.9, 125.1, 121.5, 121.4, 46.7, 42.8, 42.7, 38.3, 38.0, 12.8, 11.9. HRMS (ESI): calcd for $C_{23}H_{30}N_4O_5Na$ [M + Na]$^+$, 465.2114; found, 465.2127.

Solvent Screening Conditions with TBAF-Mediated Phoc Deprotection (Table 2). The following general procedure was used to determine the solvent effect unless otherwise stated: a solution of carbamate **2a** (0.5 mmol, 1.0 equiv) in dry THF (5 mL) was stirred at room temperature under argon. A freshly prepared 1 M solution of TBAF (1.2 equiv) in THF was added. After 1 h, water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, dried, and evaporated to dryness. The conversion and ratio were determined by comparison of the ^{1}H NMR spectra of starting material **2a** and the pure sample of amine **1a** and the corresponding symmetric urea **3aa**.

TBAF Equivalent Screening Conditions with TBAF-Mediated Phoc Deprotection (Table 3). The following general procedure was used unless otherwise stated: a solution of carbamate **2a** (0.5 mmol, 1.0 equiv) in dry THF (5 mL) was stirred at room temperature under argon. A freshly prepared 1 M solution of TBAF (X equiv) in THF was added, and the reaction mixture was stirred at room temperature until complete consumption of starting materials monitored by TLC. Then water (10 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, dried, and evaporated to dryness. The conversion and ratio were determined by comparison of the ^{1}H NMR spectra of starting material **2a** and the pure sample of amine **1a** and the corresponding symmetric urea **3aa**.

Substrate Screening for TBAF-Mediated Phoc Deprotection (Table 4). The following general procedure was used unless otherwise stated: a solution of carbamate (0.5 mmol, 1.0 equiv) in dry THF (5 mL) was stirred at room temperature under argon. A freshly prepared 1 M solution of

https://doi.org/10.1021/acsomega.2c04979
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TBAF (1.2 equiv) in THF was added. After 1 h of stirring, water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, dried, and evaporated to dryness. Purification was performed using silica column flash chromatography for **3bb**.

*1,3-Dipentylurea (**3bb**).* Yield: 45 mg (89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.71 (t, J = 5.0 Hz, 2H), 2.95 (q, J = 6.6 Hz, 4H), 1.40−1.17 (m, 12 H), 0.87 (t, J = 7.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): d = 158.5, 39.6, 30.2, 29.1, 22.4, 14.4. Chemical and spectroscopic data are identical to those from a previous report.[21]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04979.

^{1}H NMR and ^{13}C NMR spectra of the solvent effect and TBAF equivalent effect and ^{1}H NMR and ^{13}C NMR spectra of Phoc and urea compounds including ^{1}H NMR and ^{13}C NMR coalescence spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the University Paris Cité and the French "Centre National de la Recherche Scientifique". We thank Dr. S. Bouaziz (CNRS UMR 8015 Paris Cité University) for NMR experimentations.

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https://doi.org/10.1021/acsomega.2c04979
ACS Omega 2022, 7, 44861−44868