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Synthesis of linear *O*-aryl carbamates and *S*-thiocarbamates *via* benign T3P-mediated condensation of phenols and thiols with amines and carbon dioxide†

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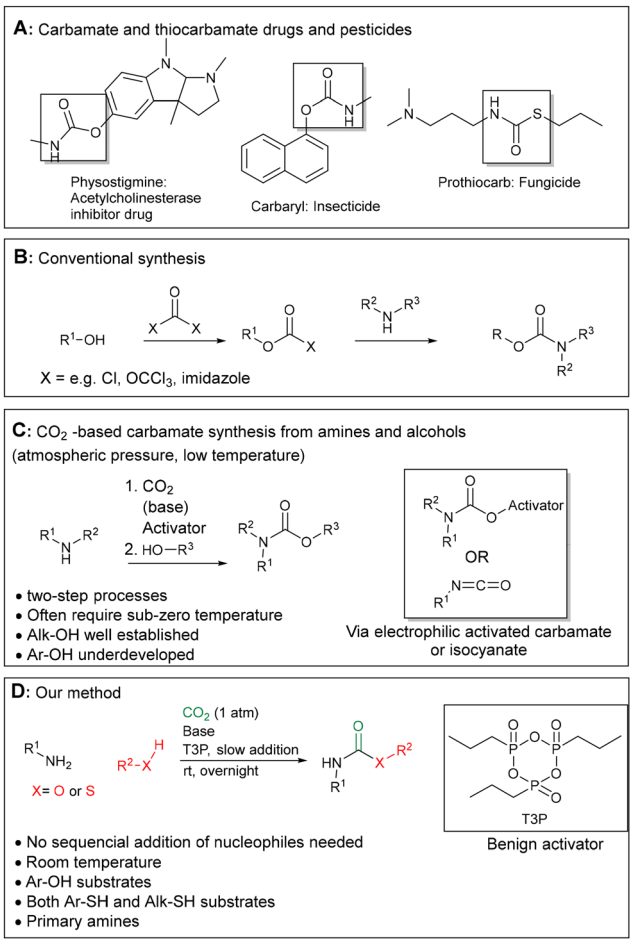
Linear (thio)carbamates are important molecules in agrochemical and pharmaceutical contexts. However, their synthesis typically involves the use of toxic reagents. Here, we present a benign method to synthesize *O*-aryl carbamates starting from phenols, primary amines, carbon dioxide and a peptide coupling reagent propanephosphonic acid anhydride (T3P) at atmospheric CO_2 pressure and room temperature. The scope was extended to thiols, yielding aryl- and alkyl *S*-thiocarbamates under similarly mild conditions.

Introduction

Linear (thio)carbamates are an important class of molecules used extensively in pharmaceuticals and pesticides (Scheme 1A).[1,2] Industrially they are often prepared from phosgene or isocyanates which are both highly toxic. In laboratory scale synthesis, phosgene is often replaced with safer phosgene derivatives such as triphosgene or carbonyldiimidazole (Scheme 1B). CO_2 has proved to be an excellent alternative carbonyl source. It is an abundant and non-toxic C1 source that has been used for numerous conversions, including carbamate synthesis.[3] Many existing methods for carbamate synthesis from CO_2, alcohols and amines require high pressure and temperature and often a metal catalyst to drive the necessary dehydration.[4–7] Such methods are less accessible for routine laboratory synthesis because of the need of specialized catalysts and equipment. The harsh reaction conditions may also cause unwanted side reactions limiting the scope. Methods that use the same starting materials but proceed at ambient pressure and relatively low temperature (<100 °C) are much less common (Scheme 1C). They require activation of a carbamate anion/carbamic acid (formed respectively by a reaction of an amine with CO_2 in the presence or absence of an external base), by a stoichiometric activator. Several methods to activate the oxygen on the carbamate anion/carbamic acid have been employed by our group and others.[8–15] However, most such



Scheme 1 Applications and synthesis of carbamates and thiocarbamates.

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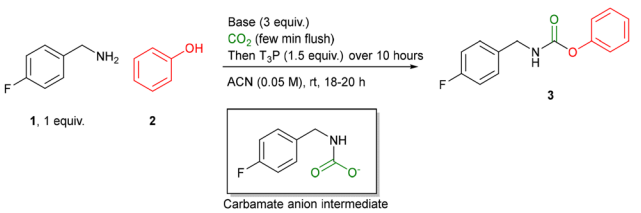
methods only work for amino alcohol substrates to form cyclic carbamates. There are only a handful of methods for linear carbamate formation at ambient CO_2 pressure when using alcohols and amines as the starting materials.[12–16] Most of these methods can only be applied for synthesis of *O*-alkyl carbamates with only a few methods that can also produce *O*-aryl carbamates.[14,15] CO_2-based syntheses of *O*-aryl carbamates that utilize other aryl substrates than aryl alcohols are also quite rare.[17–21]

Very recently, we used a peptide coupling reagent propanephosphonic acid anhydride (**T3P**) for the synthesis of cyclic carbamates from amino alcohols and CO_2.[22] **T3P** is a great choice as an activator because it is safe (low toxicity, moderate sensitization) and easy to remove with just a simple extraction.[23,24] Our success with cyclic carbamates prompted us herein to investigate the use of **T3P** as an activator for forming linear carbamates, especially the elusive *O*-aryl carbamates (Scheme 1D). In addition to those, we envisioned that thiols and thiophenols could be used instead of alcohols to synthesize thiocarbamates. Such synthetic protocols are underdeveloped, with only a few examples in the literature.[8,25,26] Importantly, to our knowledge, no published method exists for the preparation of *S*-aryl thiocarbamates directly from thiophenols, amines and CO_2.

Table 1 *O*-aryl carbamate reaction optimization



Entry	Phenol **2** (equiv.)	Base	Yield of **3** (%)
1[a]	1.1	Cs_2CO_3 + 20% DBU	13
2[b]	1.1	Cs_2CO_3 + 20% DBU	0
3	1.1	Cs_2CO_3 + 20% DBU	57
4[c]	1.1	Cs_2CO_3 + 20% DBU	42
5	1.5	Cs_2CO_3 + 20% DBU	67
6	1.5	DBU	26
7	1.5	Cs_2CO_3	71
8	1.5	K_2CO_3	3
9	1.5	TEA	13
10[d]	1.5	Cs_2CO_3	27
11[e]	**1.5**	**Cs_2CO_3**	**71**
12[e]	2.0	Cs_2CO_3	70
13[e,f]	1.5	Cs_2CO_3	68
14[e,g]	1.5	Cs_2CO_3	42

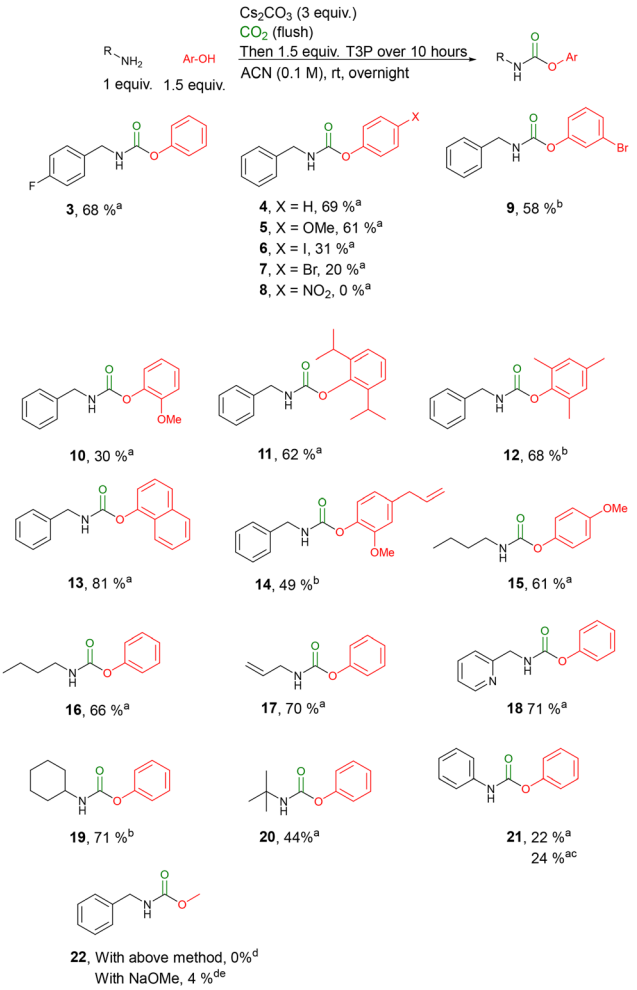
[a] DMF as the solvent. [b] DMSO as the solvent. [c] 1.1 equiv. **T3P**. [d] 2 equiv. Cs_2CO_3. [e] 0.1 M. [f] 2 equiv. of **T3P**. [g] **T3P** added dropwise over 1 min.

Results and discussion

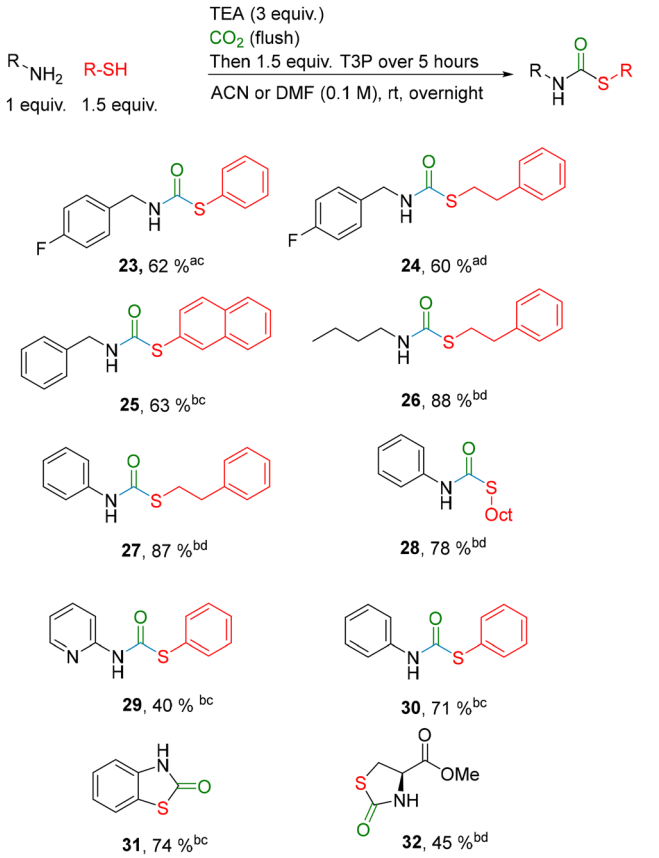
We began by studying the *O*-aryl carbamate formation using 4-fluorobenzylamine **1** and phenol **2** by applying conditions from our previous study.[22] In that study, catalytic DBU was beneficial as it increased the solubility of the carboxylated amino alcohol. Selected optimization results are shown in Table 1 (for details, see ESI, sections 4.2 and 4.3†). Acetonitrile as solvent proved superior over DMF and DMSO (entries 1–3). Decreasing **T3P** from 1.5 to 1.1 equiv. was detrimental (entry 4). Increasing the amount of phenol **2** to 1.5 improved the yield (entry 5). A base screen revealed that catalytic DBU was not needed and that Cs_2CO_3 alone was the optimal base (entries 6–9). This is very likely because in **1** and **2** remained fully dissolved upon CO_2 addition and would therefore not benefit from the solubilizing ability of DBU. Using only 2 equiv. of Cs_2CO_3 was detrimental (entry 10). Doubling the concentration did not affect the yield (entry 11). Further increase in the amount of phenol **2** or **T3P** did not improve the results (entries 12 and 13). Finally, addition of **T3P** dropwise over 1 min rather than over 10 h decreased the yield significantly (entry 14).

With the optimal conditions on hand, the scope of the *O*-aryl carbamate synthesis method was investigated (Scheme 2). Good yields were achieved with phenols bearing hydrogen, electron-donating or mildly electron withdrawing groups in the *ortho*- and *para*-positions (**3–5**, **10–13**). *para*-Positioned halides gave diminished yields, and more electron withdrawing NO_2 gave no carbamate product (**6–8**). A higher yield was achieved with halide in *meta*-position (**9**). This result indicates that yields are strongly dependent on the electronic character of the phenol, with electron-poor phenols reacting slowly and having poor selectivity towards the carbamate product over competing symmetrical urea. For example, in the synthesis of **3** only traces of symmetrical urea was detected while the yield of symmetrical urea rose to 48% in synthesis of **5** and 82% in synthesis of **7**. Accordingly, electron-withdrawing *ortho*-methoxy gave a diminished yield (**10** and **14**), while the larger methyl and isopropyl groups in the same position did not seem to have a detrimental effect (**11** and **12**). Other primary alkyl amines gave yields like those with benzylamine (**15–20**), although the yield with *tert*-butyl amine (**20**) was noticeably lower likely due to steric hinderance. Primary aryl amines worked poorly under the reaction conditions (**21**). Replacing Cs_2CO_3 with a stronger base, DBU, did not improve the yield of **21**, indicating that the low yields are likely not caused by inefficient carbamate anion formation. The low yield with the aryl amine is a combination of low selectivity towards the carbamate product over corresponding symmetrical urea (yield of urea was 26% and 35% for Cs_2CO_3 and DBU reactions respectively) and degradation of the product during reaction and isolation (ESI, section 5.2.3†). Secondary amines failed to yield *O*-aryl carbamates. This behavior is discussed later in this work.

Attempts to synthesize *O*-alkyl carbamates failed and resulted in the recovery of only symmetrical urea and unreacted alcohol (ESI, section 5.4†). Even when using alkoxide as both the base and the nucleophile, only trace amount of *O*-alkyl carbamate **22** was isolated along with a large amount of symmetrical urea. It is likely that alkyl alcohols are not



Scheme 2 Substrate scope of *O*-aryl carbamates. Synthesis was done at scales of 1.6–3.2 mmol. All yields are isolated. For detailed experimental procedures and data, see ESI, section 5.† [a]3.2 mmol scale. [b]1.6 mmol scale. [c]DBU used in place of Cs_2CO_3. [d]0.8 mmol scale. [e]4 equiv. solid NaOMe used in place of the Cs_2CO_3 and phenol.



Scheme 3 Substrate scope of *S*-thiocarbamates. Synthesis was done at a 1.6 mmol scale. All yields are isolated. For detailed experimental procedures and data, see ESI, section 5.† [a]0.8 mmol scale. [b]1.6 mmol scale. [c]ACN as solvent. [d]DMF as solvent. Oct = octane.

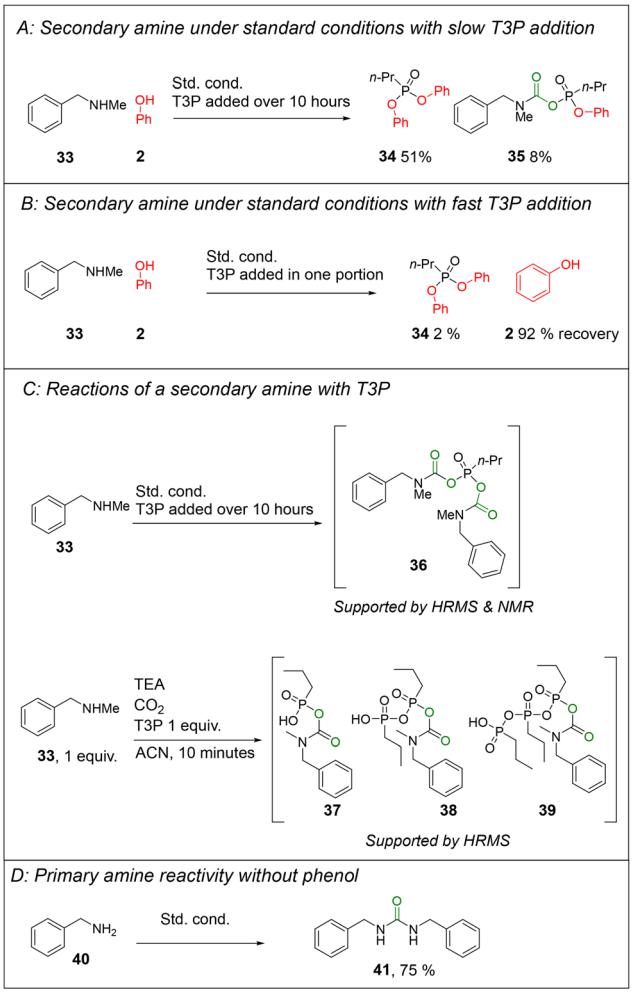
deprotonated under the reaction conditions and therefore their nucleophilicity remains too low to compete against symmetrical urea formation.

Next, we turned our attention to thiocarbamates (Scheme 3). The original conditions were largely applicable, with only minor changes. The addition time of **T3P** could be halved to 5 hours without adversely affecting the yield, and triethylamine (TEA) was the optimal base. For alkyl thiols, changing the solvent to DMF provided slightly better yields. For details, see ESI, Tables S3 and S4.†

The thiocarbamate synthesis was well-compatible with aryl and alkyl thiols and various amines, such as benzylamines (**23**–**25**), butyl amine (**26**), and even aniline (**27**, **28** and **30**), providing good to excellent yields. The latter is in contrast with the *O*-aryl carbamate method, where only low yields could be obtained. The heterocyclic aromatic amine, 2-aminopyridine, also worked and gave a modest yield (**29**). Amino thiols formed cyclic thiocarbamates (**31** and **32**).

Having established the reaction scope, we proceeded to study the reaction mechanism. First, we investigated why secondary amines fail to give any detectable amounts of carbamates. For experimental details, see ESI, section 6.† Secondary amine *N*-methylbenzylamine **33** was subjected to standard conditions with 1.5 equiv. of phenol **2** (Scheme 4A). This resulted in formation of phosphonate **34** (51%), carbamoyl phosphonate **35** (8%), and unreacted **2** (19%). In total, these compounds accounted for 77% of the amount of phenol **2** introduced at the beginning. Next, the reaction conditions were altered so that **T3P** was added in one portion instead of slowly over 10 hours. Surprisingly this time we detected only trace formation of compound **34** along with high recovery of phenol.

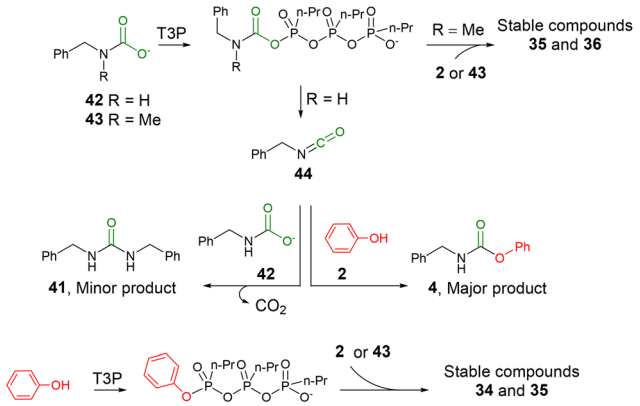
To better understand the identity of the species that form between **T3P** and the carbamate anion of secondary amine **33**, the reaction was performed in the absence of phenol **2** (Scheme 4C). Under standard condition we detected formation of the expected carbamoyl phosphonate product **36** as the major component. Unlike the similar compound **35**, compound **36** could not be isolated in pure form but both NMR and HRMS are consistent with the structure. When **T3P** was added in one portion to a solution containing the carbamate anion of **33** and allowed to react for only 10 minutes, analysis



Scheme 4 Studies on the reactivity difference between primary and secondary amines. Yields are given as the theoretical maximum yield of the product in question. See ESI, section 6† for detailed experimental data.

by HRMS showed masses corresponding to carbamoyl phosphonate species **37**, **38** and **39**. TEA was used instead of Cs_2CO_3 to achieve a clear solution and avoid problems caused by fine particles. After 2 hours, the signal of **39** had almost completely vanished while **37** and **38** persisted (ESI section 6.4†). This suggests that **39** is the most reactive of the forming intermediates. Repeating the experiment with phenol instead of carbamate of **33**, showed corresponding phenol addition products (ESI, section 6.5†).

From Scheme 4A–C and our related investigations (ESI section 6.4–6.6†) it can be concluded that **T3P** reacts rapidly with the carbamate anion of secondary amine **33** and phenol **2** to form intermediates like **37–39**. These intermediates slowly react with the available nucleophiles to form stable compounds **34–36**. In an excess of phenol **2**, the products **36** and **35** convert slowly to **34** which explains the observed product distribution in Scheme 4A (ESI, section 6.6†). If **T3P** is added in one portion, most available nucleophiles are immediately bound, quenching the formation of **34–36**. On the other hand, if **T3P** is



Scheme 5 Mechanistic proposal.

added slowly over 10 hours, there is a large excess of nucleophiles present, and compounds **34–36** form more readily.

Finally, we studied the reactivity of primary amines. When primary amine **40** was reacted under standard condition in the absence of phenol **2** (Scheme 4D), only symmetrical urea product **41** was obtained in good yield. HRMS investigation showed no sign of primary amine derived carbamate **T3P** intermediates similar to the carbamoyl phosphonates **37–39**, indicating that such species are more labile (ESI, section 6.4†).

From our findings we suggest a mechanism for the reaction (Scheme 5). Under standard conditions, primary amine derived carbamate anion **42** reacts with **T3P** to form a highly reactive carbamoyl phosphonate intermediate. This carbamoyl phosphonate can dehydrate to form isocyanate **44** which immediately reacts with phenol **2** to produce the carbamate product **4**. Reaction of **44** with another equivalent of carbamate anion **42** produces symmetrical urea **41** which is detected in significant amounts when the phenol coupling partner is of reduced nucleophilicity (such as *para*-halogenated phenols).

Secondary amine derived carbamate anion **43** reacts with **T3P** to form carbamoyl phosphonate species **37–39**. These species are still mildly activated but prefer nucleophile attack on the neighboring phosphorus center rather than the carbonyl. Therefore, instead of forming carbamate or urea with phenol **2** or carbamate anion **43**, the carbamoyl phosphonate species **34** and **35** are formed instead.

Finally, phenol **2** reacts with **T3P** to form phosphonate intermediates (ESI, section 6.5†) which can further react with phenol **2** or carbamate anion **43** to form compounds **34** and **35**. Under excess of phenol, carbamoyl phosphonates **35** and **36** convert to the more stable phosphonate **34** which is observed as the main product under standard condition with secondary amine **33** (Scheme 4A).

Conclusions

In conclusion, we have developed a method that produces linear *O*-aryl carbamates and *S*-thiocarbamates from phenols and thiols, primary amines, and carbon dioxide utilizing the

safe and convenient peptide coupling reagent **T3P** as an activator. Moderate to good yields of *O*-aryl carbamates are achieved with most primary alkyl amines and electron rich phenols. The method does not tolerate electron poor phenols, likely due to their decreased nucleophilicity. Moderate to excellent yields of thiocarbamates were achieved with primary aryl and alkyl amines and both aryl and alkyl thiols. Secondary amines are incompatible with either synthesis protocol because their **T3P** reaction intermediates like **37–39** prefer nucleophilic attack on a neighboring phosphorus center rather than the carbonyl, forming species **35** and **36** instead of the desired carbamate or urea. Despite the limitations, our method is well suited for safe and convenient synthesis of various *O*-aryl and *S*-alkyl carbamates/thiocarbamates and, to best of our knowledge, provides the first example of direct synthesis of *S*-aryl thiocarbamates from thiophenols, amines and CO_2.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.†

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