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Synthesis of Tertiary Amines Through Extrusive Alkylation of Carbamates

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Abstract

Basic amines are key elements of many biologically active natural products and pharmaceuticals. Given their inherent reactivity, it is often necessary to protect basic amines during target-directed synthesis, which results in wasteful protection/deprotection sequences. We report a step-economical approach enabling the protection of secondary amines as carbamates prior to their conversion to tertiary amines via the formal extrusion of CO_2. This method is applied to the synthesis of iboga alkaloids (±)-conodusine A and (±)-conodusine B.

Graphical Abstract

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Author Contributions

GZ and AJP optimized the reaction. GZ, WC, DF, and RNI assessed substrate scope. GZ completed the total synthesis of conodusine A and B with assistance from DF. The supporting information was prepared by WC with assistance from DF, GZ, and RNI. DEO conceived the project and wrote the manuscript with assistance from GZ, DF, and RNI.

ASSOCIATED CONTENT

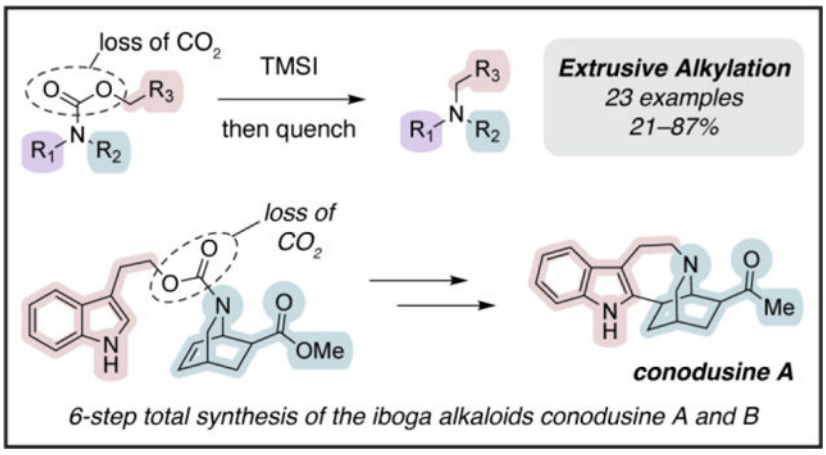
SUPPORTING INFORMATION

Detailed Synthetic Procedures and Experimental Data for all Compounds (PDF)

^{1}H and ^{13}C NMR Spectra (PDF)

Disclosure

DEO is a co-founder of Delix Therapeutics, Inc. and serves as the chief innovation officer of head of the scientific advisory board. Delix has licensed technology from UC Davis related to analogs of iboga alkaloids.



Many biologically active small molecules, including psychoactive alkaloids and central nervous system (CNS) therapeutics, contain basic amines.[1] While these highly reactive functional groups often play essential roles in binding to protein targets, they can prove quite challenging to carry through multi-step synthetic sequences given their propensities for reacting with electrophiles,[2] poisoning metal catalysts,[3,4] and complicating purification via column chromatography.[5] As a result, many synthetic chemists employ protecting group strategies to mitigate issues associated with the reactivity of basic amines. However, these approaches often prioritize synthetic tractability over atom, step, and/or redox economy.[6,7,8] Thus, methods capable of attenuating amine reactivity without adding additional deprotection steps to synthetic sequences are highly desirable.

To solve this fundamental issue, we reasoned that protection/deprotection sequences could be obviated if an amine derivative with attenuated reactivity could be directly converted into the desired basic amine product at a later point in the synthesis (Figure 1). Given their low basicity and modular construction,[9] carbamates emerged as ideal precursors for realizing such a transformation. Thus, we set out to achieve the formal extrusion of CO_2 from a carbamate starting material with concomitant formation of a C–N bond—a one-step process that we have termed extrusive alkylation. Other extrusive bond-forming reactions have been described recently,[10,11,12,13,14,15,16] though such skeletal editing strategies represent relatively unexplored retrosynthetic disconnections.

Early work from Jung and Lyster revealed that carbamates could be readily converted into amines using trimethyl silyl iodide (TMSI).[17] Presumably, this reaction proceeds through the intermediacy of a silyl carbamate and produces an alkyl halide byproduct.[18] In principle, the identification of conditions conducive to both the liberation of the amine from the silyl carbamate and S_N2 alkylation of this amine with the newly formed alkyl halide could enable a one-pot extrusive alkylation. However, after a comprehensive literature search, we found no examples of such a process, though two reports demonstrated that alkyl iodides generated from TMSI-mediated deprotection of carbamates could react further with nucleophiles if multi-step strategies were employed utilizing distinct reaction conditions for the carbamate deprotection and alkylation reactions.[19,20]

In our hands, quenching the reaction with acid led exclusively to the deprotected secondary amine product, and we ascribe this reaction outcome to rapid decarboxylation of the carbamic acid followed by protonation of the newly formed amine (Figure 2). However, we hypothesized that basic reaction conditions might enable the interception of the alkyl iodide byproduct by the liberated amine. In fact, deprotection of silyl carbamates with fluoride produces carbamate anions that can undergo *O*-alkylation under specific conditions to yield cyclic carbamates.[21] To achieve our desired C–N bond formation, we needed to identify reaction conditions that would facilitate loss of CO_2 without negatively impacting the subsequent S_N2 reaction. As the decarboxylation of carbamic acids is known to proceed through zwitterionic intermediates,[22] we quenched the reaction with a small amount of aqueous NaOH and were pleased to observe the formation of the desired tertiary amine in 13% yield (Figure 2).

Optimization of a one-pot carbamate extrusive alkylation involved identifying conditions suitable for both TMSI-mediated carbamate cleavage (phase 1) and amine alkylation (phase 2) (Table 1). Reaction of carbamate 1 with TMSI in a variety of solvents at room temperature afforded phenethyl iodide 3 in modest yields. We decided to further optimize the reaction in acetonitrile in the hopes that this solvent would prove suitable for the subsequent S_N2 reaction.[23] Fortunately, heating the reaction to reflux for 3 h resulted in clean conversion to 3 (Table 1, entry 4), and the reaction could be drastically accelerated by heating at 125°C in the microwave (MW) (Table 1, entry 5).

After identifying optimal conditions for carbamate cleavage, we explored various reaction quenches to achieve *N*-alkylation in a single reaction vessel. At the completion of the carbamate cleavage, the reaction was cooled to room temperature, quenching reagents were added, and the reaction allowed to stir for an additional 12 h. To our surprise, fluoride sources (e.g. TBAF, KF) proved largely ineffective, which we ascribe to an inability to facilitate carbamate anion decarboxylation (Table 1, entries 6–7). The use of dry K_2CO_3 also did not yield appreciable amounts of the desired amine 5a. However, we noticed a dramatic improvement in yield upon the addition of 1 equivalent of water (Table 1, entry 10). Increasing the amount of water to 3 equivalents yielded optimal reactivity (Table 1, entry 12), with additional equivalents of water proving deleterious for the S_N2 reaction.

With fully optimized conditions for the one-pot procedure, we decided to examine the scope of this transformation (Figure 3). Substrates for extrusive alkylation can be easily prepared by treating the corresponding alcohols with carbonyldiimidazole (CDI) or trisphosgene followed by an appropriate amine (see supporting information for details). Initial efforts began by examining the extrusive alkylation of various piperidine-derived carbamates (5a–5j), which proceeded in good to modest yields (42–87%). Carbamates derived from a diverse array of amines were also effective substrates for extrusive alkylation (5l–5r), including those derived from dialkylamines (5l, 5o, 5p, 5q, 5s), morpholines (5m), anilines (5n), and tetrahydropyridines (5r). In all cases, minimal amounts of overalkylation were observed.

Extrusive alkylation of cyclic carbamates leads to ring contraction and can be used to construct N-alkylated pyrrolidines (5t), azetidines (5u), and aziridines (5v). Literature examples producing these nitrogen-containing heterocycles through intramolecular

cyclization of amino alcohols are rare.[24,25] Our method obviates the need for transition metal catalysis, which is commonly employed in modern methods for synthesizing pyrrolidines, azetidines, and aziridines.[26,27,28,29,30]

The utility of extrusive alkylation of carbamates is emphasized by its broad substrate scope and functional group tolerance. Tolerated functional groups include olefins (5c, 5d, 5f, 5r, 5t, 5u, 5v), electron-rich aromatic groups (5i, 5j, 5n, 5o), heterocyles (5k), alkynes (5h), halogens (5e, 5r), ethers (5m, 5n, 5o), silyl groups (5h), vinyl halides (5r), amides (5r), and esters (5q, 5s). The method is sufficiently mild that chiral amino acids are not epimerized (5s) and aryl methyl ethers are not deprotected. Remarkably, TMSI reacts selectively with carbamates in the presence of amides or esters (5q, 5r, 5s).

This methodology works particularly well when the alcohol component can be converted into a relatively reactive electrophile, making primary, allylic, propargylic, and benzylic alcohols ideal starting materials. Carbamates derived from secondary alcohols do not tend to perform well unless they produce activated electrophiles upon reaction with TMSI (e.g. allylic 2° alcohols like 5d). Moreover, the yields of extrusive alkylation reactions tend to suffer when volatile intermediates are produced following TMSI-mediated carbamate cleavage (e.g., methyl iodide and dimethylamine as in 5r and 5l, respectively). Currently, it is unclear why carbamates derived from primary amines produce a complex mixture of products, as these carbamates are known to be readily deprotected with TMSI.[17]

To highlight the utility of this methodology, we used it to synthesize the iboga alkaloids conodusine A (11) and conodusine B (12) in only 6 steps. These alkaloids were isolated in 2016 from the stem-bark extract of *Tabernaemontana corymbose*.[31] Long before 11 and 12 were identified as natural products, the Buchi and She groups synthesized these alkaloids in 13 and 11 steps, respectively, as part of their total synthesis efforts towards ibogamine.[32,33] Since their isolation in 2016, the only other synthesis of 11 or 12 has been a semi-synthesis from catharanthine completed by the Han group in 6 steps.[34] Like many other iboga alkaloids, 11 and 12 possess three key structural features—indole, tetrahydroazepine, and isoquinuclidine ring systems.[35]

Several research groups, including those of Buchi,[32] Sames,[36] Fukuyama,[37] and Batey[38] have constructed the bicyclic isoquinuclidine core of iboga alkaloids through intermolecular Diels-Alder reactions. However, due to the inherent instability of alkyl dihydropyridines, less reactive *N*-acyl or vinylogous amide starting materials were required. We reasoned that a strategy employing extrusive alkylation would enable attenuation of dihydropyridine reactivity prior to the key C–N bond forming step without adding unnecessary protection/deprotection steps (Scheme 1). Moreover, a Diels-Alder reaction producing a thermodynamic mixture of endo and exo products would enable access of both 11 and 12 from the same starting materials.

Synthesis of 11 and 12 commenced with the reaction of commercially available tryptophol 6 and triphosgene to generate the corresponding chloroformate. Subsequent addition of pyridine and $NaBH_4$ to the reaction vessel led to the formation of dihydropyridine 7. Use of DCE as the solvent proved optimal for conducting both reactions in the same flask.

The unpurified material was subjected to Diels-Alder cyclization with methyl acrylate to produce 8 in 40% yield over 2 steps as a mixture of epimers (2:1 endo:exo). The mixture was subjected to TMSI-mediated extrusive alkylation to yield intermediate 9 in 87% yield. As expected, based on our previous extrusive alkylation studies, we did not observe any epimerization of the methyl ester.

To forge the C–C bond between the indole and isoquinuclidine, we employed two approaches. First, we utilized a metal-mediated olefin arylation originally developed by Trost[39] which was also used by Sames and co-workers[36] in their synthesis of ibogamine. While this method did enable construction of the desired C–C bond, we found the reaction to be highly variable producing 10 in yields ranging from 10– 40%. To address this issue, we were inspired by the work of Sinha and co-workers[40] and performed a reductive Heck reaction following halogenation of the indole at C2. This method proved much more reliable, consistently producing 10 in 63% yield over 2 steps (combined yield of both epimers). Finally, methyl esters 10a and 10b were transformed into the corresponding methyl ketones by forming the Weinreb amides in situ followed by addition of methyl Grignard to yield conodusine A (11) and B (12) in 65% and 57%, respectively.

The extrusive alkylation of carbamates provides an attractive, step-economical strategy for attenuating nitrogen reactivity during multi-step syntheses without introducing unnecessary protection/deprotection sequences. This methodology is broadly applicable to a variety of diverse substrates, exhibits excellent functional group tolerance, and produces the desired 3° amines in good to modest yields. The effectiveness of this method is underscored by its enablement of a 6-step synthesis of the natural products conodusine A (11) and B (12)—a step count that is half that of previous de novo total syntheses.[32,33] Taken together, this work emphasizes that relatively unexplored skeletal editing strategies can serve as powerful retrosynthetic disconnections to improve efficiency.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT

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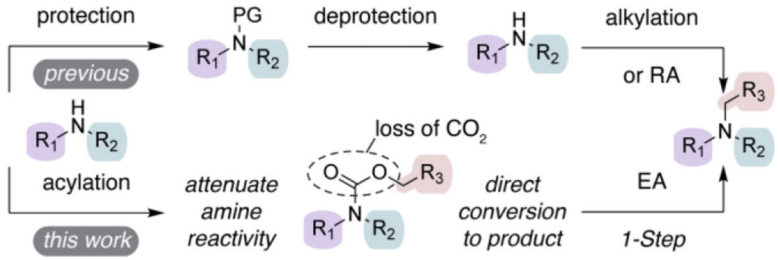


Figure 1.

Protection/deprotection sequences increase the overall step-counts of syntheses involving basic amines. In contrast, amine acylation followed by extrusive alkylation provides a more step-economical strategy for attenuating amine reactivity prior to C–N bond formation. PG = protecting group, RA = reductive amination, EA = extrusive alkylation.

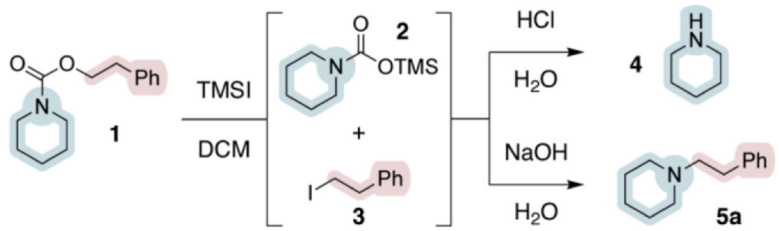


Figure 2.

Distinct products of TMSI-mediated carbamate deprotection are produced following acidic and basic quenches. An acidic quench yielded 4 and 5a in 66% and 0% yield, respectively. A basic quench yielded 4 and 5a in 73% and 13% yield, respectively.

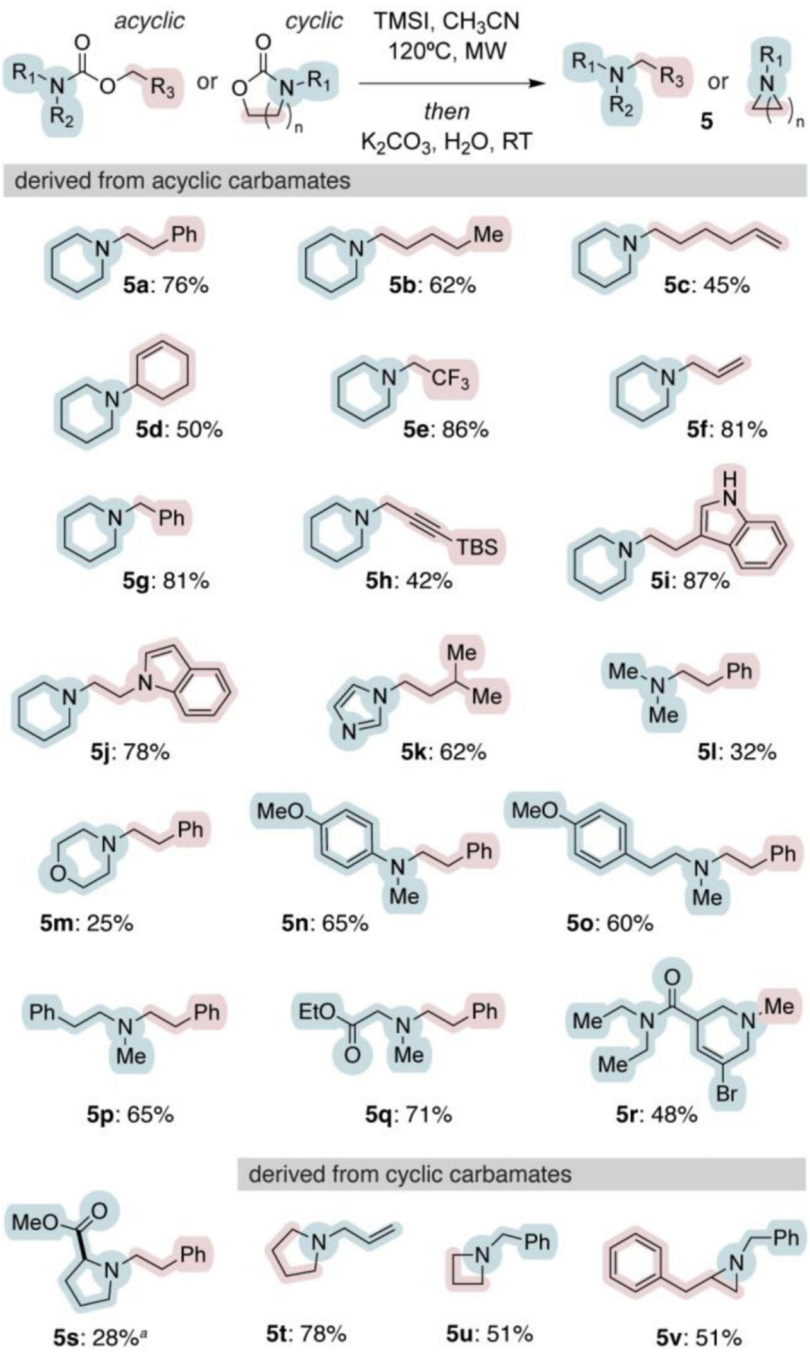
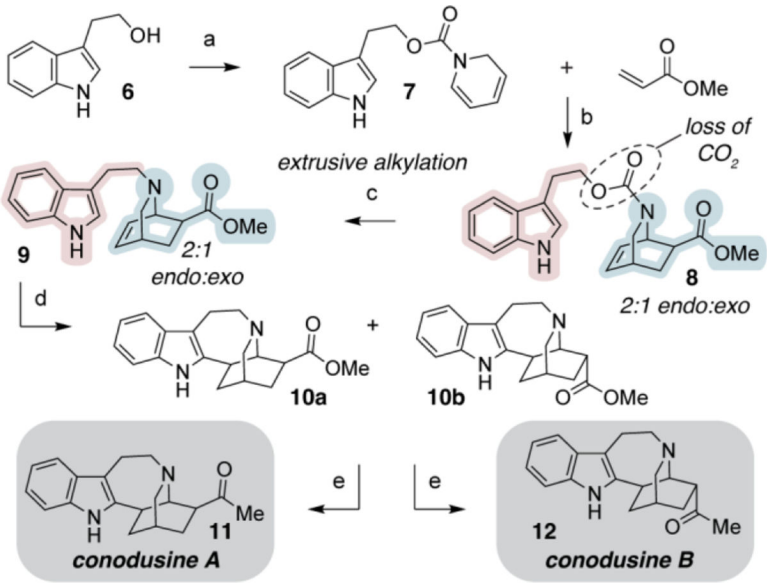


Figure 3.

The extrusive alkylation of carbamates exhibits broad substrate scope and functional group tolerability. [a]Product 5s was derived from enantiopure proline methyl ester, and no epimerization was observed by chiral LC-MS during carbamate formation or extrusive alkylation.



Scheme 1. Total Synthesis of Conodusine A and B[a]

[a]Conditions: (a) $CO(OCCl_3)_2$, Et_3N, DCE, 0°C, then C_5H_5N, $NaBH_4$ (unpurified) (b) neat, 80°C; 40% over 2 steps (c) TMSI, CH_3CN, 120°C MW, then K_2CO_3, H_2O, RT; 87%. (d) $PhNMe_3Br_3$, DCM (unpurified), then 10% $Pd(PPh_3)_4$, $NaCO_2H$, DMSO, 63% over 2 steps (combined yield of the two epimers) (e) $CH_3NH(OMe)$, MeMgBr, THF, 0°C; 11 = 65%; 12 = 57%.

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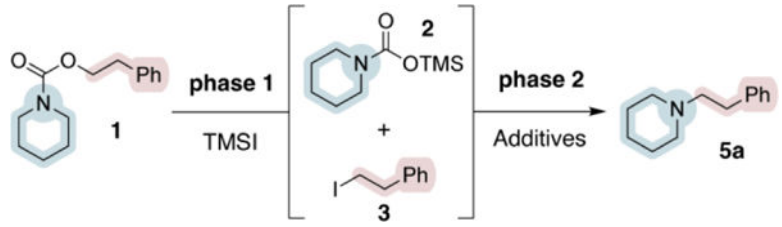
Table 1.

Optimization of a one-step extrusive alkylation



	Phase 1 (Carbamate Cleavage)			Phase 2 (Amine Alkylation)		
Entry[a]	**Solvent**	**Temp / Time**	**% Conversion 3**[c]	**Additive**[d]	**H2O (equiv)**	**% Conversion 5a**[c]
1	DCM	RT / 3 h	20	-	-	-
2	C_6H_5N	RT / 3 h	12	-	-	-
3	CH_3CN	RT / 3 h	31	-	-	-
4	CH_3CN	82°C / 3 h	>99	-	-	-
5[b]	CH_3CN	125°C / 15 min	>99	-	3	4
6[b]	CH_3CN	125°C / 15 min	>99	TBAF	0	11
7[b]	CH_3CN	125°C / 15 min	>99	KF	0	36
8[b]	CH_3CN	125°C / 15 min	>99	K_2CO_3	0	10
9[b]	CH_3CN	125°C / 15 min	>99	KF	3	34
10[b]	CH_3CN	125°C / 15 min	>99	K_2CO_3	1	27
11[b]	CH_3CN	125°C / 15 min	>99	K_2CO_3	2	33
12[b]	CH_3CN	125°C / 15 min	>99	K_2CO_3	3	68 (65)[e]
13[b]	CH_3CN	125°C / 15 min	>99	K_2CO_3	4	63
14[b]	CH_3CN	125°C / 15 min	>99	K_2CO_3	5	56

[a]Reactions were performed at 0.22 M with 2 equiv of TMSI.

[b] Step 1 was performed in a microwave.

[c] Conversion determined by ^{1}H NMR using CH_2Br_2 as an internal stancard.

[d] Three equiv of additive were used.

[e] Isolated yield shown in parentheses.