Pictet–Spengler reactions in multiphasic supercritical carbon dioxide/CO_2-expanded liquid media. *In situ* generation of carbamates as a strategy for reactions of amines in supercritical carbon dioxide†

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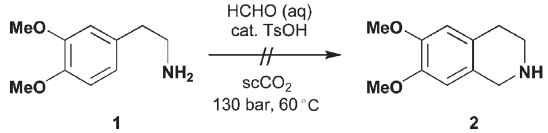
Acyl-Pictet–Spengler cyclizations can be achieved in $scCO_2$/CO_2-expanded liquid media *via* the *in situ* formation of carbamate derivatives of β-arylethylamines.

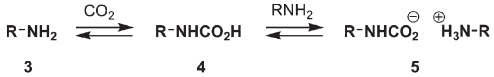
Supercritical carbon dioxide ($scCO_2$) has attracted considerable attention in recent years as an alternative to conventional solvents for organic synthesis.[1] This interest has been motivated by environmental and health considerations, as carbon dioxide is relatively nontoxic and nonflammable, inexpensive and widely available, and poses minimal problems with regard to waste disposal. The tunable solvent properties of $scCO_2$ have also attracted interest, as relatively small changes in temperature and pressure often allow for significant changes in viscosity, density, and self-diffusivity.[1] The successful application of $scCO_2$ as a reaction solvent for a variety of synthetic transformations is now well documented. We have reported on the rates and selectivities of Diels–Alder[2] and dipolar cycloadditions[3] in $scCO_2$, and have also developed protocols for effecting several Pd-catalyzed reactions in carbon dioxide.[4] Other useful transformations that can be achieved in this green solvent include a number of oxidation reactions,[5] catalytic hydrogenation,[6] olefin metatheses,[7] and enzyme-catalyzed organic reactions.[8] To date, however, only a few examples have been reported of carbon–nitrogen bond formation in $scCO_2$,[4e,9] principally due to the facility of the reaction of amines with this electrophilic solvent (*vide infra*). One goal of our program is the development of general strategies for the utilization of amines (and amine derivatives) in $scCO_2$, and the application of these strategies in C–N bond-forming reactions and the synthesis of nitrogen heterocycles. Herein we report the results of our study on the Pictet–Spengler cyclization in multiphasic $scCO_2$/CO_2-expanded liquid media, and the development of a successful strategy for effecting this important reaction in $scCO_2$ that should be applicable to other C–N bond-forming processes as well.

The Pictet–Spengler reaction is an important method for the synthesis of isoquinoline and indole alkaloids.[10] The valuable medicinal properties associated with tetrahydroisoquinolines and tetrahydro-β-carbolines continues to fuel interest in the synthesis of these classes of heterocycles. In the Pictet–Spengler reaction, these ring systems are produced *via* the cyclization of iminium ions generated *in situ* by the condensation of aldehydes with β-arylethylamines. Our initial attempts to achieve Pictet–Spengler reactions in $scCO_2$ were unsuccessful. For example, reaction of amine **1** with formaldehyde using $scCO_2$ led to a mixture of oligomeric products and none of the desired tetrahydroisoquinoline(eqn (1)). This result was not surprising, as



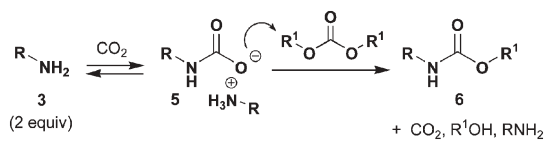
1 **2** (1)

it is well-documented that nucleophilic amines react with carbon dioxide to form carbamic acids of type **4** and ammonium carbamate salts of type **5** (eqn (2)).[11] In the presence of $scCO_2$, amine **1** is thus intercepted prior to reaction with the aldehyde, and subsequent condensation of **4** and **5** with HCHO leads to the formation of the observed oligomeric products.



3 **4** **5** (2)

The reactivity of CO_2 toward basic amines poses a significant challenge that complicates the application of many nitrogen-heterocycle forming reactions in $scCO_2$. One goal of our research has been to devise strategies for suppressing this process without interfering with the ability of the amine to participate in the desired C–N bond-forming reactions. In this initial study, we focused our attention on the protection of amines as their less nucleophilic *carbamate* derivatives which we expected to be inert to CO_2 but still competent in the subsequent heterocyclization reaction. Particularly attractive to us was the prospect of converting our amine substrates to carbamates *in situ*,[12] thus utilizing CO_2 as both a reagent and solvent for the reaction. Since alkyl halides[12a] and tin reagents[12b] are unattractive from an environmental point of view, we turned to the use of dimethyl carbonate (DMC) as a "green methylating agent"[13] for the *in situ* conversion of amines to methyl carbamates as formulated in eqn (3) (R^1 = Me).[14]



3 (2 equiv) **5** **6** + CO_2, R^1OH, RNH_2 (3)

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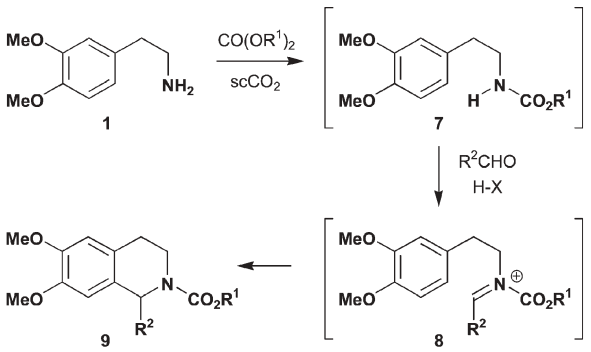
† Electronic supplementary information (ESI) available: Description of reaction apparatus and experimental procedures and characterization data for **14–21** and **24**. See http://dx.doi.org/10.1039/b508151c



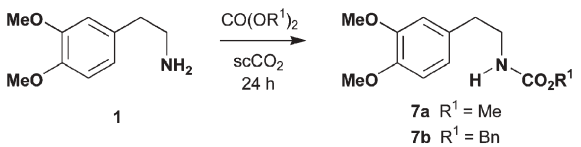
Scheme 1 Strategy for *in situ* protection of amines and Pictet–Spengler cyclization.

Scheme 1 outlines the application of this strategy for effecting reactions of amines in CO_2 in the context of the Pictet–Spengler reaction. Reaction of **1** with CO_2 would generate an ammonium carbamate salt, which upon alkylation with DMC would produce the carbamate **7**. Condensation with an aldehyde (in the presence of acid) would then furnish the iminium ion intermediate **8**, which would undergo cyclization to afford the desired Pictet–Spengler product. An added benefit of this approach is that N-acyliminium ions such as **8** are known to exhibit enhanced reactivity in Pictet–Spengler cyclizations.[15]

Reactions were carried out in a Thar stainless steel view cell reactor (25 mL internal volume) that allows visual inspection *via* two coaxial sapphire windows. Cell pressure and temperature were monitored with a pressure gauge and internal thermocouple probe. Temperature set-points were achieved using a controller interfaced with insulated heating tape wrapped tightly about the exterior cell wall. Reactor contents were mixed using a magnetic stir bar.

Table 1 summarizes the results of our optimization of conditions for the *in situ* generation of carbamates **7a** and **7b** from **1**. In a typical reaction, a biphasic system forms consisting of a lower

Table 1 Optimization of carbamate synthesis



Entry	Carbonate (equiv.)[a]	*T*/°C	*P*/bar	Product	Yield (%)[b]
1	DMC (1.1)	130	120–130	**7a**	48
2	DMC (1.5)	130	120–130	**7a**	62
3	DMC (2.0)	130	120–130	**7a**	66
4	DMC (7.5)	130	120–130	**7a**	77
5	DMC (1.5)	130	~1[c]	**7a**	47
6	DMC (1.5)	130	95–100	**7a**	55
7	DMC (1.5)	130	180–190	**7a**	55
8	DMC (2.0)	100	120–130	**7a**	54 (77)[d]
9	DMC (2.0)	110	120–130	**7a**	56 (62)[e]
10	DMC (2.0)	150	120–130	**7a**	61
11	DBC (2.0)	130	120–130	**7b**	69

[a] DMC = dimethyl carbonate, DBC = dibenzyl carbonate. [b] Isolated yields of products purified by column chromatography. Yields determined to be reproducible to ±1%. [c] Reaction in a sealed tube under CO_2. [d] Corrected yield based on 75% conversion of **1**. [e] Corrected yield based on 90% conversion of **1**.

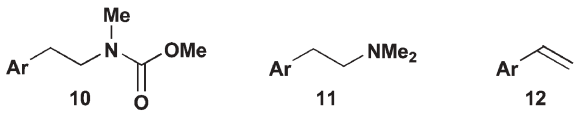


Fig. 1 Side products from reaction of **1** with DMC in the presence of $scCO_2$ (Ar = 3,4-dimethoxyphenyl).

density supercritical-like CO_2 phase and a higher density CO_2-rich liquid phase, the latter containing dialkyl carbonate and the ammonium carbamate salt derived from reaction of **1** with CO_2. After 24 h at 130 °C, complete conversion of **1** was observed leading in quantitative yield to a mixture of **7a** and the side products **10**, **11**, and **12** (Fig. 1). Thus, a critical issue was to maximize the alkylation of the intermediate carbamate salt **5** (leading to the desired product) relative to the competing N-alkylation of the amine starting material (which was shown to be responsible for the formation of these side products).[16]

The equilibrium formulated in eqn (2) should be shifted further toward **5** with an increase in the concentration of CO_2 in the CO_2-expanded liquid phase, leading to an increase in the selectivity for alkylation of the carbamate salt **5** over alkylation of amine **3**. Dimethyl carbonate readily absorbs carbon dioxide,[17] and so an increase in the amount of DMC employed results in an increase in the amount of CO_2 in the liquid DMC/ammonium carbamate salt phase. This leads to an increase in selectivity for the desired alkylation, and thus an improved yield of **7a** (Table 1, entries 1 to 4). The concentration of MeOH byproduct, which has been shown to lower the selectivity for carbamate formation,[14c] is also reduced when more DMC is employed. Improved yields of **7a** were also observed with increasing CO_2 pressure, which similarly promotes carbamate salt formation *via* an increase in liquid phase CO_2 concentration[17] (compare entries 2, 5, and 6). It is noteworthy that the selectivity for **7a** decreases at very high pressures (entry 7) where the DMC partitions from the liquid phase into the blanket $scCO_2$ phase, resulting in a smaller volume of DMC in the liquid phase (verified visually), and thus a lower concentration of CO_2 in this phase. Selectivity for **7a** over **10–12** increases at lower temperatures (entry 8), possibly due to (a) increased absorption of CO_2 into the liquid phase at lower temperatures,[17] and/or (b) slower N-methylation of the amine at temperatures $\leqslant$100 °C.[13] However, alkylation of the ammonium carbamate salt is also sluggish at 100 °C resulting in incomplete conversion after 24 h. Finally, entry 11 demonstrates that this strategy for the *in situ* protection of amines in $scCO_2$ can also be extended to the formation of *benzyl carbamates* by substituting dibenzyl carbonate (DBC) for DMC. The utility of Cbz derivatives as protective groups for amines is well established.

We next turned our attention to examining the use of the *in situ* generated carbamates as substrates for acyl-Pictet–Spengler reactions in a triphasic system consisting of a supercritical-like CO_2 phase, a CO_2-rich liquid phase, and a H_2O-rich liquid phase. Table 2 delineates the scope of this two-stage strategy for effecting acyl-Pictet–Spengler reactions of β-arylethylamines. Typical conditions involve treating the amine with dialkyl carbonate in $scCO_2$ at 130 °C (120–130 bar) for 24 h, cooling the resulting reaction mixture to 80 °C, and then adding the aldehyde and acid (1.5 equiv.) *via* a pressurized injection loop. Further reaction at 80 °C for 24 h then affords the desired tetrahydroisoquinolines.

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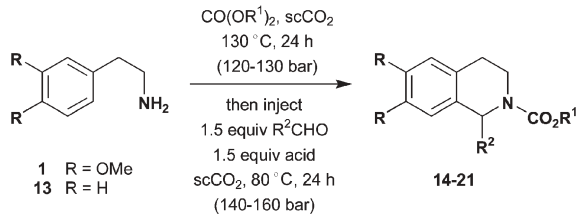
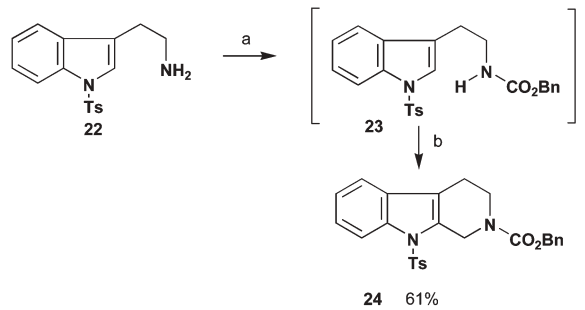
Table 2 Synthesis of tetrahydroisoquinolines



Entry	Amine	Carbonate R^1 (equiv.)	R^2	Acid[a]	Product	Yield (%)[b]
1	**13**	Me (2.0)	H	H_2SO_4	**14**	52
2	**1**	Me (2.0)	H	H_2SO_4	**15**	54
3	**1**	Me (2.0)	H	TFA	**15**	62
4	**1**	Me (7.5)	H	H_2SO_4	**15**	63
5	**1**	Me (2.0)	Ph	H_2SO_4	**16**	56
6	**1**	Me (7.5)	Ph	H_2SO_4	**16**	69
7	**1**	Me (2.0)	*i*-Pr	H_2SO_4	**17**	53
8	**1**	Me (7.5)	*i*-Pr	H_2SO_4	**17**	71
9	**1**	Me (2.0)	CO_2Me[c]	H_2SO_4	**18**	49
10	**1**	Bn (2.0)	H	TFA	**19**	67
11	**1**	Bn (2.0)	Et	TFA	**20**	71
12	**1**	Bn (2.0)	Ph	H_2SO_4	**21**	57

[a] 9.0 M H_2SO_4 or 50% v/v TFA in H_2O. [b] Isolated yields of products purified by column chromatography. [c] Reaction with $(MeO)_2CHCO_2Me$ as methyl glyoxylate equivalent.



Scheme 2 Synthesis of tetrahydro-β-carbolines *via* Pictet–Spengler reaction. (a) 5 equiv. $CO(OBn)_2$, $scCO_2$, 130 °C, 130 bar, 24 h; (b) add 1.3 equiv. aq. HCHO, 1.3 equiv. 50% aq. TFA, 80 °C, 160 bar, 24 h.

Both electron-neutral and electron-rich β-arylethylamines participate in the reaction, which can also be applied to a variety of aliphatic and aromatic aldehydes. Acyl-Pictet–Spengler reaction with methyl glyoxylate can be achieved by introducing this aldehyde in the form of its dimethyl acetal derivative. Trifluoroacetic acid can be employed in place of H_2SO_4 to promote iminium ion formation, and its use leads to somewhat improved yields due to the sensitivity of some carbamate groups to sulfuric acid under these conditions. Finally it was noted that the overall yield for this two-stage process improves somewhat as the volume of DMC increases from 2.0 to 7.5 equiv. relative to amine. This effect is attributed to improved selectivity for carbamate formation over N-methylation as discussed above.

Scheme 2 illustrates the extension of the acyl-Pictet–Spengler reaction in multiphasic $scCO_2/CO_2$-expanded liquid media to include the synthesis of tetrahydro-β-carbolines. Reaction of tryptamine **22**[18] with CO_2 and DBC affords **23** which reacts with HCHO in the presence of TFA to furnish **24** in 61% overall yield.

The application of this general strategy for utilizing amines in other C–N bond-forming reactions in environmentally-friendly media is under investigation.

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