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Mono-acylation of piperazine and homopiperazine via ionic immobilization

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ABSTRACT

A method for the selective mono-acylation of piperazine and homopiperazine has been developed. In a flow system, initially the diamine is ionically immobilized on a sulfonic acid funtionalized silica gel, acylated with an appropriate reagent and finally liberated with ammonic methanol. Examples with high yield and purity are presented.

Mono-protected diamines are valuable synthetic intermediates and have found use in drug-discovery,[1] combinatorial[2] and macromolecule[3] synthesis. Traditional methods for the mono-acylation of diamines in which both nitrogens exhibit similar (or identical) reactivity often rely upon stoichiometric manipulation—typically a large excess of the diamine relative to the acylating agent.[4,5] This strategy is less than ideal if the diamine is valuable and/or of limited supply. Additionally, a large excess of a reactant can lead to isolation and purification challenges.

The solid-phase immobilization of diamines via covalent bond formation followed by acylation then cleavage has successfully produced mono-acylated diamines.[6] Unfortunately, there are several drawbacks to this approach; notably the expense of functionalized resins for organic synthesis, the decreased reaction rates on solid phase (vs solution-phase chemistry), and finally, the need for two additional synthetic steps (resin binding and cleavage). This Letter details a new method for the mono-acylation of diamines which mitigates or eliminates the shortcomings of both solution-phase and traditional solid-phase approaches.

The past decade has seen tremendous progress in the concepts and applications of solid-phase extractions (SPE) as purification techniques.[7] Notable among the various solid supports utilized for SPE has been the emergence of silica-based strong cation exchange (SCX) chromatography. In a typical SCX application, a post-reaction mixture in a neutral solvent is passed through a cartridge containing a SCX sorbent (often a silica backbone functionalized with a sulfonic acid containing hydrocarbon). The basic components within the mixture undergo an acid-base reaction with the immobilized acid, forming immobilized salts. The acidic and/or neutral components within the mixture are washed through the cartridge with neutral solvent. Finally, if the basic component(s) from the original mixture is desired, the cartridge is flushed with a solution basic enough to compete off the desired component(s)—this has been coined '*catch and release purification*'.[8] Interestingly, to date there are no known reports of successful covalent bond formation on SCX ionically immobilized substrates.

In the initial investigations, homopiperazine (**1a**) in methanol was loaded into a disposable cartridge of SCX.[9] After a rinse sequence which transitioned the solvent to 100% DCM, the **1a** loaded cartridge was treated with $(Boc)_2O$ (**2a**). The solvent system was transitioned back to 100% methanol, and the cartridge was eluted with ammonia in methanol. Gratifyingly, evaporation of the ammonic eluent provided essentially pure homopiperazine-1-carboxylic acid *t*-butyl ester (**3a**). The output of this SCX supported mono-acylation of **1a** was optimized through a series of titrations,[10] and iterative solvent and cartridge diameter explorations.[11] This exercise resulted in the following general procedure.

General procedure: A SCX cartridge[9] was conditioned with MeOH (2.5 mL),[12] then diamine (0.5 M in MeOH, 300 μL, 150 μmol) was added. The cartridge was rinsed with MeOH (2 × 2.5 mL), 25% MeOH/EtOAc (2 × 2.5 mL), EtOAc (2 × 2.5 mL), and DCM (2 × 2.5 mL). The cartridge was then treated with an acylating agent (1.0 M in DCM, 450 μL, 450 μmol) followed by rinsings with DCM (2 × 2.5 mL), EtOAc (2 × 2.5 mL), 25% MeOH/EtOAc (2 × 2.5 mL), and MeOH (2 × 2.5 mL). Finally, the cartridge was 'eluted to collect' with NH_3 (2 N in MeOH, 3 mL), and the resulting solution was concentrated to dryness and placed under a 2 mmHg vacuum for 1 h.

Using the general procedure specified above, **1a** was reacted with **2a** on SCX. In a parallel reaction, piperazine (**1b**) was reacted in an identical fashion (Scheme 1). GC analyses of the unconcentrated ammonic eluents showed them to both contain the desired products (**3a** and **3b**, respectively) along with unacylated starting materials (**1a** and **1b**, respectively). Yet, in both instances, concentration of the ammonic eluents under reduced pressure provided >97% pure mono-Boc products (yields are based upon **1a** or **1b** used, purity gauged by ^1H NMR). The yields of this process, using **1a** and **2a**, were improved to 64% by treating the immobilized diamine with two portions of **2a** (1.0 M in DCM, 2 × 450 μL) and otherwise following the general procedure (similarly, an 81% yield was obtained through treatment with three portions of **2a**).

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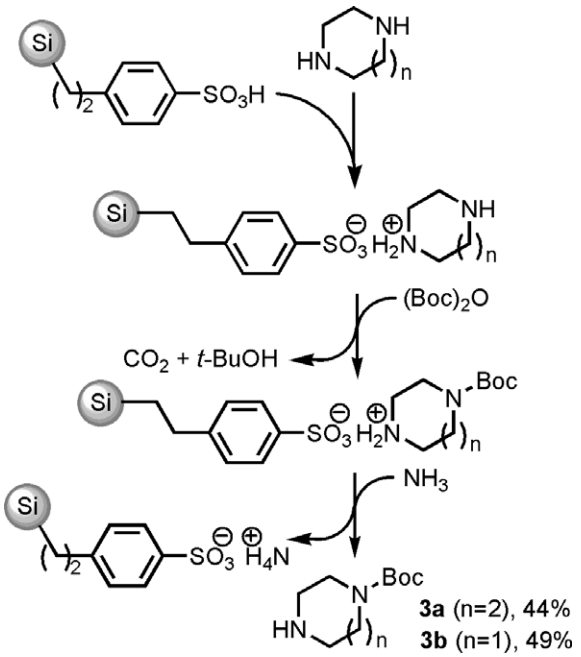


Scheme 1.

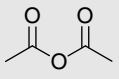
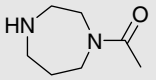
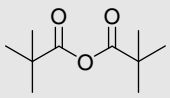
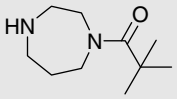
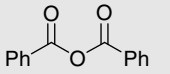
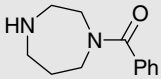
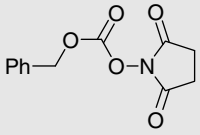
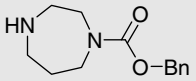
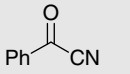
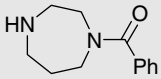
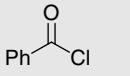
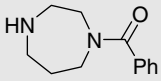
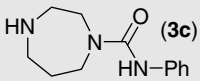
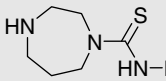
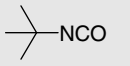
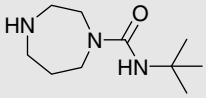
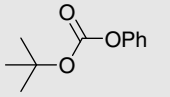
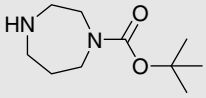
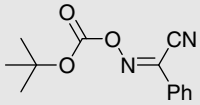
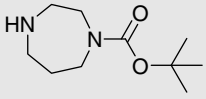
Unfortunately, other diamines examined which included propane-1,3-diamine, *N,N′*-dimethyl-propane-1,3-diamine, *trans*-cyclohexane-1,2-diamine, *trans*-*N,N′*-dimethyl-cyclohexane-1,2-diamine, and *trans*-cyclohexane-1,4-diamine failed to provide substantial yields of the desired mono-acylated products (providing predominantly unreacted starting diamine). The decreased nucleophilicity of these diamines relative to **1a** and **1b** is one possible explanation—while another intriguing possibility (for the 1,2 and 1,3-diamine systems) is that chelation of the otherwise reactive nitrogen with the proximal cationic ammonium precludes reactivity. Increasing the dwell time of the acylating agents in the presence of the immobilized diamines has the potential to overcome this limitation and is currently under investigation.

The use of acid catalysis in the solution-phase *t*-butoxycarbonylation of amines is known[13] (including catalysis with a sulfonic acid functionalized silica gel),[5] but this phenomenon is unknown with alternate (i.e., non-*t*-butyl) acylating agents. Therefore, it was of particular interest to explore the scope of this methodology with a range of acylating agents. Utilizing the general procedure above with **1a**, while varying the acylating agent, provided an interesting series of results (Table 1).

Of the 11 acylating agents examined, only two: *t*-butyl phenyl carbonate (entry 10) and 'BOC-ON', (entry 11) failed to react under these conditions. These two failures are presumed to be caused by the acylating agents mitigated reactivity relative to **2a** (but it is also possible that they failed due to their propensity to undergo acid promoted decomposition). Of all the successful acylating agents in this process, the lowest yield was obtained with benzoyl chloride (Table 1, entry 6). Acylation with benzoyl chloride produces HCl—a strong enough acid to compete with the immobilized sulfonic acid and cause the premature loss of substrates and products.

To further demonstrate the utility of this methodology, a scaled-up procedure was performed using **1a** and **2a**. This procedure was performed on 50 g of SCX,[9] which was loaded into a 34 mm inner diameter flash chromatography column. The general procedure (above) was then followed at 100× scale.[12] Thus, the SCX was conditioned with 250 mL of MeOH and treated with **1a** (0.5 M in MeOH, 30 mL, 15 mmol), then rinsed with MeOH (2 × 250 mL). This resulted in a 1.45 g yield of **3a** (48% yield, >97% pure by ^{1}H NMR).[14]

Table 1
SCX supported acylation of **1a** with various acylating agents

Entry	Acylating agent	Product	Product[a]/mg (yield[b]/%)
1			12.0 (56)
2			12.0 (43)
3			9.6 (31)
4			13.8 (39)
5[c]			17.3 (56)
6			5.8 (28)
7	Ph–NCO (**2b**)	 (**3c**)	24.8 (75)
8	Ph–NCS		15.6 (44)
9			19.4 (65)
10			No desired product
11			No desired product

[a] Yields average of two runs; all products had >95% purity by ^{1}H NMR.
[b] Yields based upon amount of **1a** used.
[c] CAUTION: HCN produced.

In conclusion, a novel methodology for the mono-acylation of diamines has been described. This system combines the selectivity and purity associated with a traditional solid-phase approach with the relative speed, yields, and scalability typified by solution-phase synthesis. Studies of this new methodology continue in an attempt to improve yields and broaden the scope of applicable diamines—including investigations of the reactivity of unsymmetrical diamines. Additional synthetic transformations which exploit ionic immobilization are currently under investigation.

Acknowledgments

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References and notes

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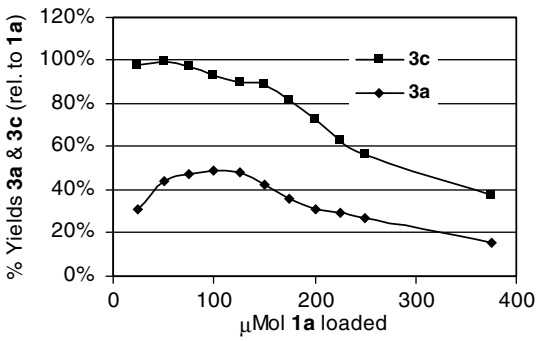
9. SCX cartridges purchased from United Chemicals Technologies, Inc. Bristol, PA USA. Product name: 'CUBCX1 (Benzenesulfonic acid)'. Specifications: 500 mg in a 3 mL cartridge (loading = 0.7 meq/g). Loose SCX (i.e., not prepackaged in cartridge format) was purchased from the same supplier (and had the same loading).
10. Titration example: the amounts of **2a** and **2b** (both 450 μmol) and SCX (0.50 g) were held constant while increasing amounts of **1a** were used. The yields of products (**3a** and **3c**) obtained are plotted against the amount of **1a** used.



11. In the reaction of **1a** with **2a** under the otherwise standard reaction conditions, the smaller the diameter of the reaction tube (i.e., the longer the SCX bed), the higher the yield of **3a**.
12. With the small SCX cartridges (0.5–1.0 g SCX), the solvents were allowed to 'gravity drain'. Upon scale-up, the solvent was forced through the SCX bed with positive nitrogen pressure.
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14. Drying time under a 2 mmHg vacuum extended to 20 h.