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1,2,3,4-Tetrahydro-γ-carbolinium salts: novel reactions with thiols, mediated by polymer-supported reagents

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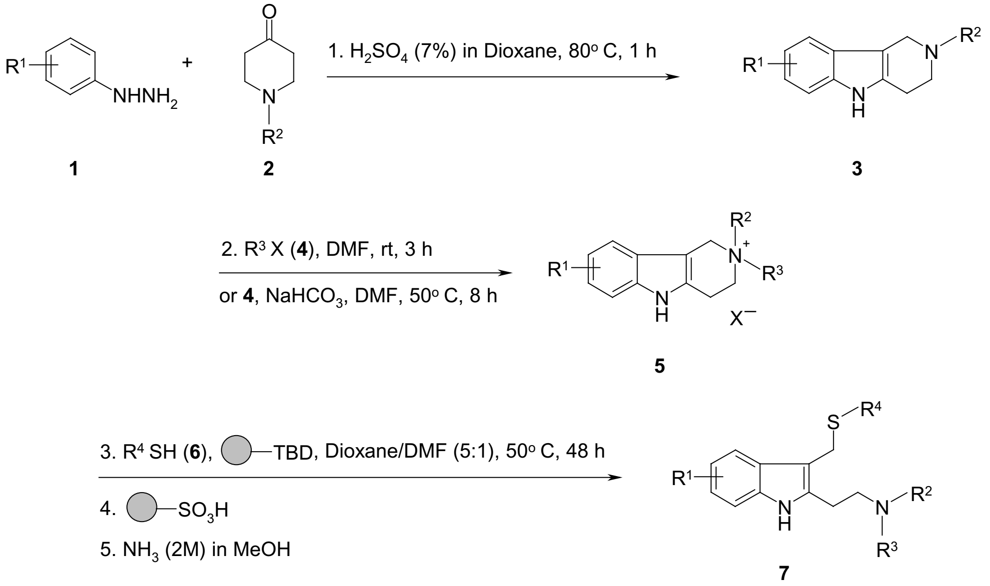
Abstract—A series of dialkyl-[2-(3-alkylsulfanylmethyl-1*H*-indol-2-yl)-ethyl]amines was produced using a novel route involving nucleophilic ring opening of 2,2-dialkyl-1,2,3,4-tetrahydro-γ-carbolinium salts with thiols. The insertion reaction was mediated by a strong, polymer-supported base, and the purification of the target compounds was facilitated using resin-bound sulfonic acid.

The reaction of 2,2-dialkyl-1,2,3,4-tetrahydro-γ-carbolinium salts with carbon-based nucleophiles has been disclosed in the literature.[1–3] However, there are no reported examples of reactions of these substrates with simple aliphatic and aromatic thiols. We have discovered that this nucleophilic ring opening reaction is a robust and versatile synthetic protocol, and can be conveniently mediated by polymer-supported reagents.

Scheme 1 illustrates the procedure developed. The Fischer cyclization of phenylhydrazine **1** (1.0 equiv) with *N*-alkyl-piperidone **2** (1.05 equiv) in a solution containing 7%



Scheme 1.

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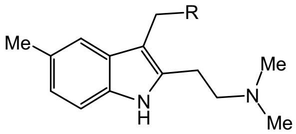
Table 1



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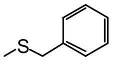
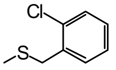
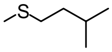
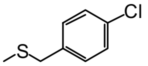
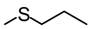
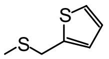
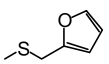
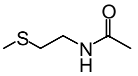
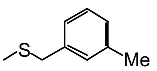
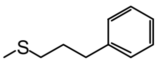
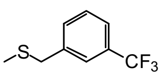
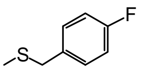
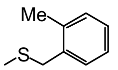
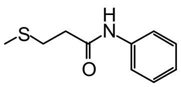
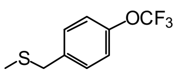
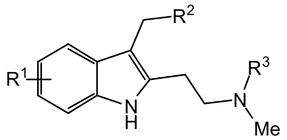
1		84
2		95
3		86
4		92
5		87
6		80
7		86
8		86
9		88
10		91
11		87
12		89
13		94
14		91
15		94

Table 2



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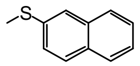
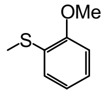
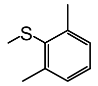
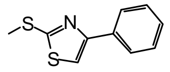
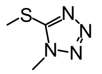
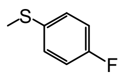
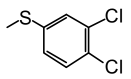
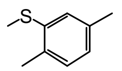
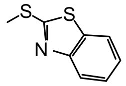
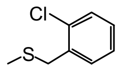
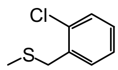
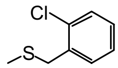
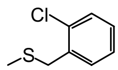
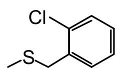
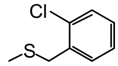
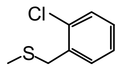
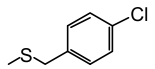
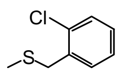
1	5-Me		Me	90
2	5-Me		Me	85
3	5-Me		Me	93
4	5-Me		Me	83
5	5-Me		Me	94
6	5-Me		Me	61
7	5-Me		Me	42
8	5-Me		Me	94
9	5-Me		Me	68
10	5,7-Di-F		Me	66
11	5-SO_2NH_2		Me	72
12	H		Me	76
13	4,6-Di-Cl		Me	77
14	5-CF_3		Me	72
15	5,7-Di-Me		Me	26
16	7-Br		Me	51
17	5-Me		4-OCF_3-Bn	70
18	5-Me		C(O)-*t*-Bu	80

concentrated sulfuric acid in 1,4-dioxane proceeded smoothly to furnish the tetrahydrocarboline **3**, typically in greater than 90% conversion.[4] Quaternization of the basic nitrogen was accomplished by treating **3** with a 1:4 v/v mixture of an alkyl halide, **4**, and *N*,*N*-dimethylformamide (DMF). An alternative method, used in cases where this procedure proved to be a little sluggish, involved treating **3** with a solution of haloalkane and DMF (1:5 v/v ratio) in the presence of 5 equiv of sodium bicarbonate, and warming to 50 °C; the desired intermediate was then isolated following filtration. A solution of the tetrahydrocarbolinium salt (**5**) in DMF was then added to a stirred suspension containing 2 equiv each of a thiol, **6**, and polymer-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)[5] in 1,4-dioxane, and the resulting reaction mixture was agitated at 50 °C for 2 days. The suspension was then filtered, and the filtrate poured onto sulfonic acid resin (5 equiv).[6] After 30 min, the resin was washed thoroughly with methanol, and the desired product, **7**, was isolated following treatment of the resin with a 2 M solution of ammonia in methanol, followed by evaporation of the resulting filtrate under reduced pressure. Table 1 highlights the results obtained using a range of sulfur-based nucleophiles using this protocol.[8]

As part of a broader exercise, we subsequently examined a series of reactions incorporating additional sulfur-based nucleophiles with a varied set of substrates (Table 2). Generally, these insertion reactions proceeded smoothly as had been observed previously, though we did notice that, unlike with the majority of analogues synthesized in this study, some of the products resulting from thiophenol insertions tended to gradually decompose following isolation. Further, reactions involving electron-poor thiols gave less clean product mixtures. We were also interested to discover that insertion reactions involving 2-benzyl mercaptan with indole ring-substituted substrates also proceeded with good conversion.

In summary, this short communication illustrates the first reported example of nucleophilic ring opening reactions of 2,2-dialkyl-1,2,3,4-tetrahydro-γ-carbolinium salts with thiols. The reaction is a valuable route into a diverse array of sulfide derivatives, and can be mediated by supported reagents, making it a useful synthetic procedure for parallel synthesis.

References and notes

1. Diker, K.; Maindreville, M. D.; Lévy, J. *Tetrahedron Lett.* **1995**, *36*, 3511–3512.
2. Sapi, J.; Grébille, Y.; Laronze, J.; Lévy, J. *Synthesis* **1992**, 383–386.
3. Zinnes, H.; Schwartz, M. L. U.S. (1976), US 3931229 19760106 Application: US 74-458916 19740408; CAN 84:90000; AN 1976:90000.
4. For the original report outlining the construction of tetrahydro-γ-carbolines, see: (a) Cook, A. D.; Reed, K. J. *J. Chem. Soc.* **1945**, 402; For a more recent example of an alternative method for the construction of these heterocycles, see: (b) Zhang, L.; Meier, W.; Wats, E.; Costello, T. D.; Ma, P.; Ensinger, C. L.; Rodgers, J. M.; Jacobsen, I. C.; Rajagopalan, P. *Tetrahedron Lett.* **1995**, *36*, 8387–8390.
5. Commercially available from Polymer Laboratories Ltd, catalogue #3414-1679.
6. Commercially available from Polymer Laboratories Ltd, catalogue #3404-4679.
7. Percentage conversion to the desired products was determined by HPLC at 220 and 254 nm using an Agilent 1100 LC/MSD VL ESI system.
8. *Analytical data for Table* 1, *entry 2*: δ_H (400 MHz, $CDCl_3$) 9.45 (1H, s), 7.45–7.35 (1H, m), 7.30–7.20 (5H, m), 7.10 (1H, m), 3.92 (2H, s), 3.88 (2H, s), 3.30–3.22 (2H, m), 3.18–3.12 (2H, m), 2.75 (6H, s), 2.45 (3H, s). M+1 found 373.4; $C_{21}H_{26}ClN_2S$ requires 372.14.