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Synthesis of substituted 1*H*-imidazol-1-ylmethylpiperidines. Facile separation of 1,4- and 1,5-disubstituted imidazoles

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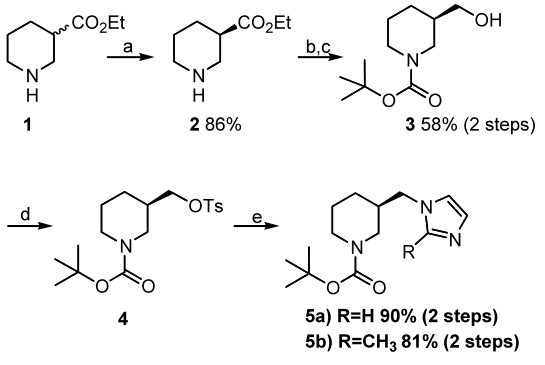
Abstract—The synthesis of several 1*H*-imidazol-1-ylmethylpiperidines is described. A method for the regioselective isolation of 1,4-disubstituted imidazoles utilizing the selective quaternization of the 1,5-disubstituted regioisomer was developed.

As farnesyl transferase has emerged as a leading target for the development of novel cancer chemotherapeutic agents many of the most potent inhibitors have been found to contain functionalized imidazoles.[1] As part of a continuing research program to identify novel farnesyl transferase inhibitors, we were interested in preparing a series of compounds containing the 1*H*-imidazol-1-ylmethylpiperidine moiety with varying substitution on the imidazole ring.

The general synthetic route to this class of compound is illustrated in Scheme 1. Resolution of ethyl nipecotate using tartaric acid,[2] followed by LAH reduction and nitrogen protection gave aminoalcohol **3**. Treatment of **3** with tosyl chloride, displacement with sodium imidazole, and deprotection gave the desired product **5a**. The corresponding 2-methyl derivative was prepared in a similar fashion by substituting imidazole for 2-methylimidazole gave the corresponding derivative **5b**.



Scheme 1. *Reagents and conditions*: (a) Ref. 1; (b) $LiAlH_4$; (c) ditertbutyldicarbonate; (d) *p*-tosyl chloride; (e) R = H, sodium imidazole; R = CH_3, NaH, 2-methyl imidazole.

While the preparation of *N*-substituted and 1,2-disubstituted imidazoles is straightforward, the regioselective preparation and separation of the 1,4- and 1,5-disubstituted imidazoles presents a more difficult problem. Direct alkylation generally gives limited enrichment of one regioisomer over the other. In rare instances, the 1,4-disubstituted analogs can be prepared by direct alkylation, but the relative efficiency is dependent on the presence of directing substitution.[3c,4] Limited examples for the preparation of the 1,4-disubstituted cases through the construction of the imidazole ring have been developed but these preparations are generally limited in scope and yield.[5]

Substantial precedent exists for the preparation of 1,5-disubstituted imidazoles.[3] Quaternization of the N4-protected triphenylmethyl imidazole with the desired electrophile and cleavage of the more labile triphenylmethyl group readily yields the 1,5-disubstituted imidazole. Successful quaternization is dependent on the use of highly electrophilic alkylating agents which is somewhat limiting to the overall breadth of the sequence.

By exploiting the propensity of the imidazole ring to undergo quaternization, we discovered an efficient method for the separation and isolation of mixtures of

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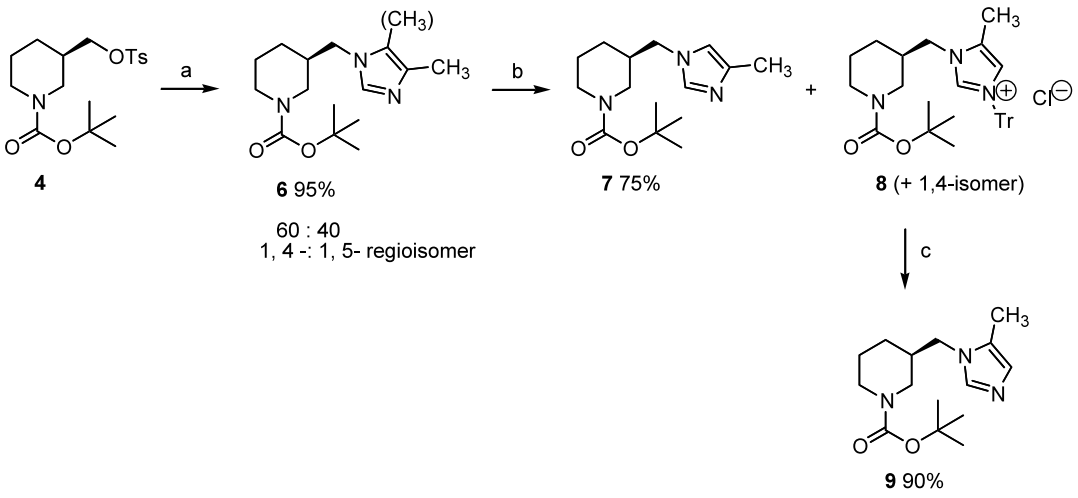

Scheme 2. *Reagents and conditions*: (a) NaH, 4(5)-methylimidazole; (b) TrCl; (c) MeOH, reflux.

1,4- and 1,5-disubstituted imidazoles. Thus, quaternization utilizing sterically encumbered yet reactive triphenylmethyl chloride, regioselectively occurs on the least hindered nitrogen and, therefore, predominates on the 1,5-disubstituted regioisomer.

In practice, direct alkylation of the intermediate tosylate **4** gave **6** as a ~60:40 mix of 1,4- and 1,5-disubstituted imidazoles, respectively, as determined by NMR (Scheme 2). Regioselective coordination of the 1,5-disubstituted imidazole with triphenylmethylchloride led to an easily separable mixture of **7** and quaternized 1,5-disubstituted imidazole **8** in good yield based on the initial composition of the mixture. While the preparation of the 1,4-disubstituted isomers were of greater interest for our program, the 1,5-disubstituted isomer **9** can be easily isolated by liberating the quaternized product by heating in methanol at reflux. Because quaternization of the 1,4-isomer does occur to some extent in the presence of excess triphenylmethylchloride adjustment of equivalents of triphenylmethyl chloride relative to the 1,4-isomer is essential for isolation of the desired regioisomer, i. e. 1.05 and 0.95 equiv. for the mixture of the 1,4- and 1,5-isomer, respectively.

This methodology was extended to a series of other disubstituted imidazoles; a few representative examples with the yield of the corresponding 1,4-disubstituted imidazole are shown in Table 1.[6] Yields are unoptimized and are reflective of the recovery of 1,4-disubstituted isomer estimated to be present in the initial mixture. The efficiency of this method does not appear to be dependent on the nature of the N1-substituent on the imidazole and yields are comparable with larger substitution on the imidazole ring.

In conclusion, we have developed a method for the efficient synthesis of 1*H*-imidazol-1-ylmethylpiperidines. The development of an efficient method for the separation of 1,4- and 1,5-disubstituted mixtures allowed for the facile preparation of a variety of pure 1, 4-disubstituted imidazole analogs.

General procedure for isolation of 1,4-disubstituted imidazoles: To a solution of **6** (0.295 mol, 60% 1,4-disubstituted regioisomer) in CH_2Cl_2 (1000 mL) at 0°C was added triphenylmethyl chloride (37.6 g, 1.15 equiv. based on 1,4-disubstituted) in one portion. The resulting solution was stirred at 0°C for 2 h and concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 and loaded onto a plug of silica gel (100×140 mm) and eluted using a 50:50 EtOAc:acetone mix as eluent to give **7** as a clear oil (37.5 g, 75% yield, based on 1,4-disubstituted regioisomer). ^{1}H NMR ($CDCl_3$): 7.32 (s, 1H), 6.61 (s, 1H), 3.79 (m, 4H), 2.7 (m, 1H), 2.22 (s, 3H), 1.89 (m, 2H), 1.69 (m, 2H), 1.45 (m, 10H), 1.20 (m, 1H); ^{13}C NMR ($CDCl_3$): 154.4, 137.3, 136.2, 115.5, 79.6, 49.7, 46.9, 44.1, 37.0, 28.3, 28.1, 24.0, 13.4; FABMS: 280 (M+H). $[\alpha]_D^{20} = -10°$ (*c* 2.5, CH_3OH). Anal. (C_{15}, H_{25}, N_3, O_2.0.05 CH_2Cl_2) C, H, N.

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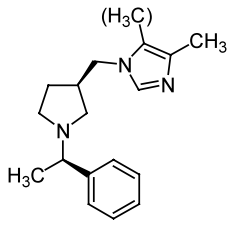
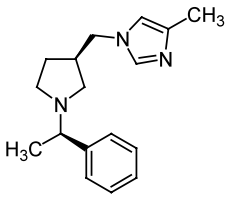
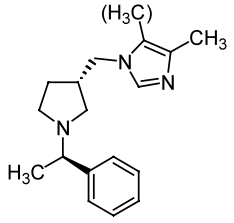
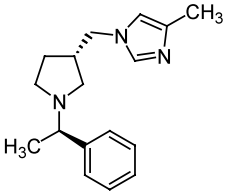
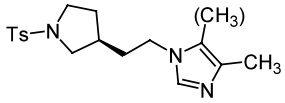
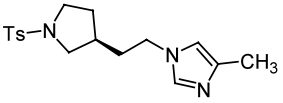
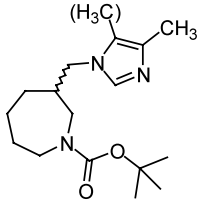
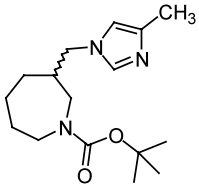
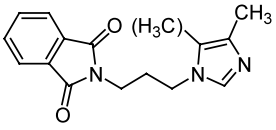
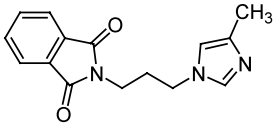
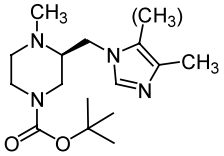
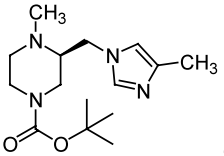
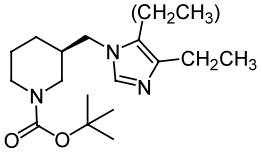
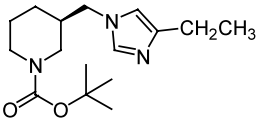
Table 1. Isolation of 1,4-disubstituted imidazoles

Entry	Starting 1,4- and 1,5- isomeric mixture	Isolated 1,4-isomer (% yield)
1		 (50)
2		 (74)
3		 (85)
4		 (61)
5		 (89)
6		 (85)
7		 (67)

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