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Parallel synthesis of substituted imidazoles from 1,2-aminoalcohols

Konrad H. Bleicher,[a] Fernand Gerber,[a] Yves Wüthrich,[a] Alexander Alanine[a] and Alfredo Capretta[b,*]

[a]*F. Hoffmann-La Roche AG, CH-4070 Basel, Switzerland*

[b]*Institute of Molecular Catalysis, Department of Chemistry, Brock University, St. Catharines, Ontario, Canada L2S 3A1*

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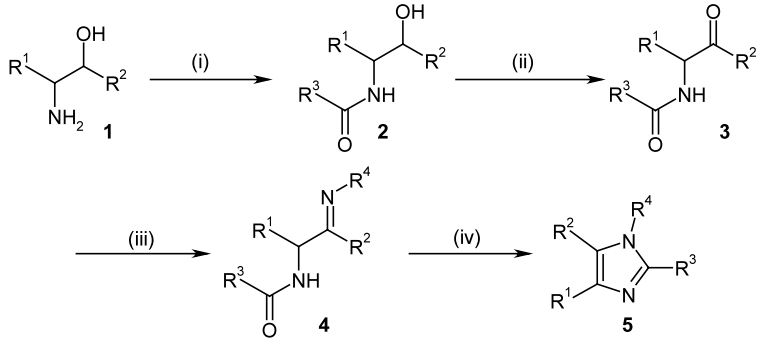
Abstract—Substituted imidazoles can be prepared efficiently from cyclic or acyclic 1,2-aminoalcohols via a four-step procedure involving acylation of the amine, oxidation of the alcohol, imine formation and cyclization. Examples are presented and the methodology is applied in the generation of a library of compounds containing a fused imidazole-azepine motif.

Imidazoles are found ubiquitously in Nature and are incorporated as key structural fragments in many biological and chemical systems.[1] While numerous syntheses of these five-membered heterocycles are described in the literature,[2] one approach to substituted imidazoles involves the use of α-amidoimines (Scheme 1, **4**).[3] Treatment of these systems with reagents (such as PCl_5; $POCl_3$; or PPh_3, C_2Cl_6, Et_3N) that allow for conversion of the amide to its corresponding chloroimine, results in cyclization to the imidazole (**5**). In the route developed by Engel and Steglich, the α-amidoimines were derived from amino acid precursors via a Dakin West rearrangement. However, other disconnections of the α-amidoimines are possible. The key imine (**4**) is clearly derived from the ketone (**3**) which in turn can come from either an α-aminoketone or the α-amidoalcohol (**2**). Removal of the acyl group reveals that the starting point for the synthesis would be the vicinal aminoalcohol (**1**). This is a particularly attractive pathway since there are established, preparative routes to these systems[4] as well as a number of 1,2-aminoalcohols commercially available.

The general synthetic route is illustrated in Scheme 1. The vicinal amino alcohols (**1**) were treated with EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) and the desired carboxylic acid to allow for amide formation in high yields.[5] Use of acid chlorides proved to be problematic since significant amounts of the bisacylated product were formed under these conditions. Utilization of EDCI also tolerated the addition of small amounts of water to the reaction mixture



Scheme 1. General synthetic route to substituted imidazoles. *Reagents and conditions*: (i) R^3-CO_2H, EDCI, CH_3CN, H_2O; (ii) SO_3·pyridine, DMSO, Et_3N; (iii) R^4-NH_2 and either Ti(*i*-PrO)$_4$, CH_2Cl_2 or Si(OEt)$_4$, H^+, toluene; (iv) PCl_5.

* Corresponding author. Tel.: +1-905-688-5550 ext. 3848; fax: +1-905-682-9020; e-mail: fcaprett@chemiris.labs.brocku.ca

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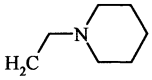
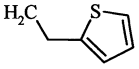
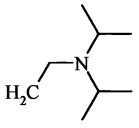
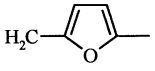
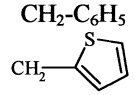
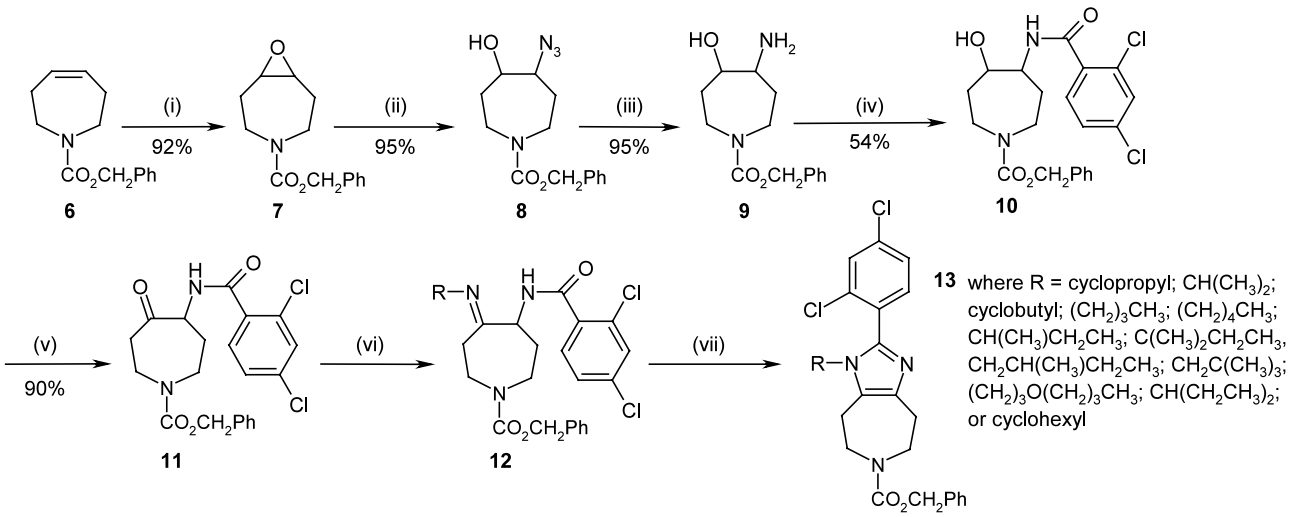
facilitating dissolution of the amino alcohols (often used as their hydrochloride salt) and smooth coupling. While numerous oxidation protocols were investigated for the conversion of **2**→**3**, a protocol utilizing sulphur trioxide pyridine complex demonstrated itself to be the most generally applicable.[6] In this way, both secondary and primary alcohols could be readily oxidized to their corresponding ketones or aldehydes in roughly 2 h in excellent yields. Not surprisingly, the ease and degree of imine formation **4** varied greatly depending on the nature of the carbonyl and amine employed. With the majority of cases (aldehydes with alkyl-, benzyl- or aryl amines and ketones with alkyl- and benzylamines), imine formation was carried out in dichloromethane in the presence of a Lewis acid.[7] In the more stubborn cases (those involving ketones and arylamines, for example **5c**), a modification of the Love and Ren's protocol,[8] involving tetraethoxysilane under acidic conditions, was used.[9] The imines were not isolated but treated directly with phosphorous pentachloride. Under these conditions, the amidoimine rapidly cyclized to the imidazole. Other reagents also induced cyclization (for example, $POCl_3$ or PPh_3, C_2Cl_6), however, the PCl_5 was shown to be the most effective. The entire procedure could be carried out without isolation or purification of the intermediates.

Phenylalaninol, 2-amino-1-(3,4-dimethoxyphenyl)propan-1-ol and 2-aminocyclohexanol were chosen as the initial vicinal aminoalcohols for investigation since this collection of substrates contains a variety of functionality (including cyclic or acyclic examples, primary and secondary alcohols, aliphatic and aromatic fragments). Similarly, the carboxylic acids (alkyl and aromatic) and the amines (alkyl-, benzyl- or aryl amines containing heteroaromatic fragments and other functionality) were selected so as to provide a broad assortment of condensation components and, thereby, illustrate the general applicability and scope of the chemistry developed. The results are summarized in Table 1 with the overall yield based on the amount of vicinal aminoalcohol used. Note that all compounds were characterized by MS, ^1H

Table 1. Substituted imidazoles prepared via Scheme 1

Entry	*aminoalcohol*		*carboxylic acid*	*amine*	overall yield (%)
	R_1	R_2	R_3	R_4	
5a	CH_3	3,4-dimethoxyphenyl	C_6H_5	$(CH_2)_3$-CH_3	64
5b	CH_3	3,4-dimethoxyphenyl	C_6H_5	CH_2-C_6H_5	57
5c	CH_3	3,4-dimethoxyphenyl	C_6H_5	C_6H_5	32
5d	CH_3	3,4-dimethoxyphenyl	CH_3	CH_2-C_6H_5	56
5e	CH_3	3,4-dimethoxyphenyl	CH_3	CH_2-$CH(CH_3)_2$	67
5f	CH_3	C_6H_5	2,4-dichlorophenyl		48
5g	CH_3	C_6H_5	2,4-dichlorophenyl		52
5h	CH_3	C_6H_5	2,4-dichlorophenyl		55
5i	CH_3	C_6H_5	2,4-dichlorophenyl		45
5j	CH_3	C_6H_5	2,4-dichlorophenyl		63
5k	CH_3	C_6H_5	2,4-dichlorophenyl	CH_2-$CH(CH_3)_2$	55
5l	CH_3	C_6H_5	2,4-dichlorophenyl	$CH_2CH{=}CH_2$	51
5m	CH_3	C_6H_5	2,4-dichlorophenyl		62
5n	CH_2-C_6H_5	H	C_6H_5		67
5o	CH_2-C_6H_5	H	C_6H_5	$CH(C_6H_5)_2$	64
5p	CH_2-C_6H_5	H	C_6H_5	CH_2-$CH(CH_3)_2$	72
5q	CH_2-C_6H_5	H	C_6H_5	4-tolyl	65
5r	-$(CH_2)_4$-		C_6H_5	$(CH_2)_3$-CH_3	76
5s	-$(CH_2)_4$-		C_6H_5		68
5t	-$(CH_2)_4$-		C_6H_5	CH_2-C_6H_5	66
5u	-$(CH_2)_4$-		C_6H_5		52



Scheme 2. Synthetic route to imidazole-azepine library. *Reagents and conditions*: (i) *m*-CPBA, CH_2Cl_2; (ii) NaN_3, acetone/H_2O; (iii) PPh_3, H_2O, THF; (iv) 2,4-dichlorobenzoic acid, EDCl, CH_3CN, H_2O; (v) SO_3·pyridine, DMSO, Et_3N; (vi) R-NH_2, Ti(*i*-PrO)$_4$, CH_2Cl_2; (vii) PCl_5.

and ^{13}C NMR.[10] Examples **5r**, **5s**, **5t** and **5u** (those derived from 2-aminocyclohexanol) were among the most intriguing as these systems represent imidazole annulations. It should be noted that while this methodology works well with six-membered cyclic systems containing the requisite 1,2-aminoalcohol moiety, exploratory efforts to carry out the same chemistry on five-membered analogues were unsuccessful.

If one considers the numerous routes available to 1,2-aminoalcohols, those originating from an alkene moiety are especially appealing. As a result, an extension of the imidazole annulation chemistry was developed during the preparation of the imidazole-azepine library shown in Scheme 2. Benzyl 2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate **6** was converted to epoxide **7** under standard *m*CPBA conditions then opened to the vicinal azidoalcohol **8** via treatment with NaN_3. Reduction to **9** proceeds well using Staudinger conditions. With the required 1,2-aminoalcohol in place, application of the chemistry developed above allows for facile introduction of the substituted imidazole fragment. Acylation with 2,4-dichlorobenzoic acid and EDCI gave **10** which was readily oxidized to **11**. Treatment with a series of amines allowed for preparation of the imines (of the general type **12**) that were cyclized to the imidazoles **13** using the chemistry described above in overall yields ranging from 50 to 62% (based on the amount of **11** employed). This family of compounds effectively demonstrates the usefulness of the methodology and shows that one can now conceive of virtually any isolated double bond as a potential site for the introduction of an imidazole.

From a medicinal chemistry point of view, the methodology developed is ideally suited for use with a wide range of readily available building blocks in a parallel fashion resulting in a combinatorial array of pharmacologically interesting small molecules. The carboxylic acid, aminoalcohol and primary amine building blocks are available commercially as collections in large sets of variable structures. Alternatively, the aminoalcohols can be accessed via amino acids or, as demonstrated above, from olefins (perhaps derived from metathesis reactions). The robustness of the chemistry developed coupled with the large set of starting materials insures an efficient library synthesis and structural diversity within these compound collections. Details concerning these imidazole libraries and the application of the chemistry to solid phase imidazole synthesis as well as solid supported reagents will be reported in due course.

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4. For examples, see: (a) Andersson, M. A.; Epple, R.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 472–475; (b) Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.
5. *General procedure for amide formation*. The aminoalcohol (1 mmol), carboxylic acid (1.1 mmol) and EDCI (210 mg, 1.1 mmol) were suspended in acetonitrile (25 ml) and sufficient water was added dropwise to allow for complete dissolution of all the reagents. The reaction mixture was stirred at room temperature for 18 h at which time the solvent was evaporated under a reduced pressure and material used directly in the following step. Alternatively, the residue could be purified by column chromatography using silica gel.
6. *General procedure for the oxidation*. The amidoalcohol (1 mmol) was dissolved in DMSO (10 ml) and Et_3N (600 mg, 6 mmol) and cooled to 0°C. The reaction mixture was then treated with a solution of SO_3·pyridine complex (477 mg, 3 mmol) in DMSO (10 ml) and allowed to warm to room temperature. After 2 h, the reaction mixture was added to CH_2Cl_2 (4×40 ml) in a separatory funnel and washed with 0.1N HCl (3×40 ml). The organic layer was then dried with sodium sulphate and evaporated under a reduced pressure. The residue could be purified by column chromatography using silica gel or used directly in the following step.
7. *General procedure for imine formation and cyclization to the imidazole*. The aldehyde or ketone (1 mmol) generated in the previous step was dissolved in CH_2Cl_2 (10 ml) and treated with the amine (2 mmol) and Ti(*i*OPr)$_4$ (284 mg, 1 mmol). The reaction mixture was stirred at room temperature for 18 h at which time PCl_5 (833 mg, 4 mmol) was added. The mixture was allowed to stir for a further 5 h. The solvent was evaporated under a reduced pressure and the residue suspended in ethyl acetate (3×20 ml) and then washed with 0.1N NaOH (3×20 ml). The organic layer was then dried over sodium sulphate, evaporated under a reduced pressure and the residue purified by column chromatography using silica gel.
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9. *Alternate procedure for imine formation and cyclization to the imidazole*. The ketone (1 mmol) and the amine (2 mmol) were dissolved in toluene (10 ml) and treated with Si(OEt)$_4$ (416 mg, 2 mmol) and a drop of conc. H_2SO_4. The solution was heated to reflux for 18 h. The reaction was then cooled to room temperature and treated with PCl_5 (833 mg, 4 mmol). The mixture was allowed to stir for a further 5 h. The solvent was evaporated under a reduced pressure and the residue suspended in ethyl acetate (3×20 ml) then washed with 0.1N NaOH (3×20 ml). The organic layer was then dried over sodium sulphate, evaporated under a reduced pressure and the residue purified by column chromatography using silica gel.
10. Representative spectroscopic data. **5a**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.86 (3H, t), 1.22 (2H, m), 1.72 (2H, m), 2.68 (3H, s), 3.81 (s, 3H), 3.83 (t, 2H), 3.94 (s, 3H), 7.10–7.76 (8H, m): ^{13}C NMR: (DMSO-d_6, 125 MHz) δ 14.4, 20.7, 25.9, 31.8, 50.2, 2×56.0, 111.9, 112.7, 124.5, 126.0, 2×126.9, 127.3, 128.2, 2×128.6, 130.2, 145.54, 148.7, 149.6, 150.5; HRMS for $C_{22}H_{26}N_2O_2$: calculated 350.1994, observed 350.1983. **5k**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.83 (6H, d), 2.68 (3H, s), 2.73 (1H, m), 3.98 (d, 2H), 7.27–7.69 (8H, m); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 2×20.6, 25.9, 34.8, 55.9, 125.8, 127.2, 2×128.2, 2×128.4, 2×128.8, 129.9, 131.8, 132.9, 133.1, 136.0, 138.2, 150.6; HRMS for $C_{20}H_{20}Cl_2N_2$: calculated 358.1004, observed 358.1009. **5r**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.76 (3H, t), 1.17 (2H, m), 1.57 (2H, m), 1.81 (4H, m), 2.65 (2H, m), 2.72 (2H, m), 3.99 (2H, t), 7.58 (3H, m), 7.75 (2H, m); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 13.6, 19.4, 20.4, 22.2, 22.3, 23.4, 31.9, 44.4, 128.7, 128.9, 2×129.1, 2×129.3, 129.4, 130.6, 143.5; HRMS for $C_{17}H_{22}N_2$: calculated 254.1783, observed 254.1790.