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Aust. J. Chem. **2011**, *64*, 1617–1620
http://dx.doi.org/10.1071/CH11358

Full Paper

Three-Component Mannich-like Reaction of 2-Aminoimidazole

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A three-component reaction of 2-aminoimidazole with various aldehydes and amines is described that generates 4-substituted 2-aminoimidazoles containing a new chiral centre, a new C–C bond and a new C–N bond. The reactions can be conducted in water and require only sodium carbonate as reagent.

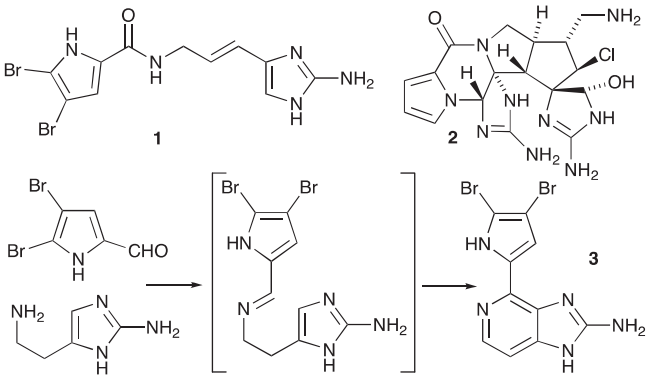
Manuscript received: 1 September 2011.
Manuscript accepted: 13 October 2011.
Published online: 22 November 2011.

Introduction

Natural products have played a pre-eminent role in drug development[1] and, more recently, as templates for focussed combinatorial libraries.[2] Similarly, multicomponent reactions that are atom-efficient and convergent approaches to diversity-orientated synthesis have been widely sought for the generation of diversity libraries.[3] In this communication, we report the first three-component Mannich-like reaction of 2-aminoimidazole (2-AI) that shows promise for the generation of natural-product-like libraries.

2-Aminoimidazole is a common structural motif in marine natural products and has itself been isolated from the sponge *Reneira cratera*.[4] Numerous examples of natural products bearing the 2-AI nucleus can be found, for example the oroidin (**1**) family of alkaloids of which >100 are currently known, many with powerful biological activity.[5] For example, Palau'amine (**2**) has been shown to have potent anticancer activity.[6] Another example is ageladine A (**3**), which has powerful antiangiogenic activity.[7] We have recently reported a concise synthesis of **3** using 2-AI in a biomimetic Pictet–Spengler reaction as the key step (Scheme 1).[8]

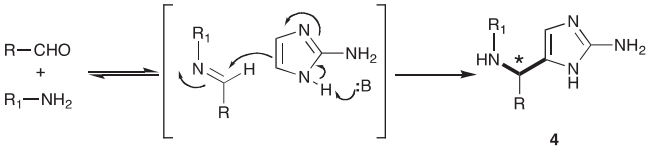
In order to increase the scope of this reaction, we envisaged a three-component version of the process in which two new bonds as well as a chiral centre are formed simultaneously (Scheme 2), presumably with the intermediacy of an imine formed from the aldehyde and primary amine. Multicomponent reactions are convergent processes where three (or more) starting materials are condensed in a cascade of elementary equilibria that terminates in an irreversible step.[9] Although a multicomponent (Mannich) Pictet–Spengler reaction has not previously been reported for 2-AI, precedent for this approach can be found in two early reports. The first, by Kato et al. in 1952,[10] reported that 4-methylimidazole and formaldehyde reacted in the presence of dimethylamine to form 4(5)-substituted imidazoles, and Forsyth[11] reported the formation of mixtures of mono-, di- and tri-substituted imidazoles from piperidine, formaldehyde and 2-methylimidazole. Forsyth[11] found that N-alkylation was favoured at low pH and C-alkylation at high pH but complex mixtures were always formed.



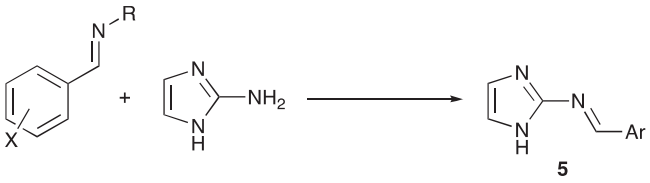
Scheme 1. Biomimetic synthesis of ageladine A using the Pictet–Spengler reaction as the key step.

Results and Discussion

Initially, we attempted a three-component reaction between 2-AI, butyl amine and acetaldehyde in the presence of scandium triflate, the conditions we used for intramolecular Pictet–Spengler reaction in the total synthesis of ageladine A.[8] This reaction failed to yield the three-component adduct, so we decided to first try to react activated imines with 2-AI (Scheme 3). Reaction of 2-AI with *N*-Tosyl-benzylimine under neutral or acidic conditions led to no observable reaction but when sodium carbonate was used as a base, a low (18 %) yield of the transimination product **5a** was observed (Table 1). This could be increased to ~50 % by using methanol as solvent and caesium carbonate as base. Using highly activated imines (e.g. 3′-nitrophenyl) gave yields over 60 % for **5b**. Disappointingly, no Mannich-like products were observed.



Scheme 2. Multicomponent Mannich reaction of 2-aminoimidazoles with amines and aldehydes. The heavy bonds indicate new bonds formed and the asterisk the new chiral centre.



Scheme 3. Reaction of 2-aminoimidazlone (2-AI) with activated imines leads to transimination.

Table 1. Reactions of 2-aminoimidazole with activated imines to form transimination products (given in parantheses)

R^A	X^A	Solvent	Base	Time [h]	Yield [%]
Tosyl	H (**5a**)	H_2O	–	24	0
Tosyl	H (**5a**)	H_2O	Na_2CO_3	24	18
Tosyl	H (**5a**)	H_2O/EtOH (9:1)	Na_2CO_3	24	32
Tosyl	H (**5a**)	H_2O/MeCN (9:1)	Na_2CO_3	24	27
Tosyl	H (**5a**)	MeOH	Cs_2CO_3	8	48
Butyl	3-NO_2 (**5b**)	MeOH	Cs_2CO_3	8	61
Butyl	2-NO_2 (**5c**)	MeOH	Cs_2CO_3	8	56

[A]R, X as per Fig. 3.

The results obtained here were quite surprising, as in our experience with the Pictet–Spengler reaction (intramolecular Mannich reaction) of 2-AI, we found that the C4(5) position of the 2-AI was more nucleophilic than the guanidine nitrogens.[8] These results suggested a balance needed to be struck between the fixed nucleophilicity of the 2-AI and the electrophilicity of the imine. While screening less activated imines, we found that the imine formed between acetaldehyde and benzylamine, when stirred overnight with 2-AI in water, gave a low (10 %) yield of the desired product (**4b**). Encouraged by this result, we attempted a three-component version by mixing 2-AI, benzylamine and acetaldehyde in water with sodium carbonate as base. After 8 h stirring, the reaction resulted in the formation of the expected three-component product **4b**, albeit in low yield (15 %), along with unreacted 2-AI (56 %). No N- or multiply alkylated products were observed. Characterization of the product by 2D NMR spectroscopy confirmed the exclusive formation of the 4-substituted product ($^3J_{CH}$ couplings between Hα and C5, and the methyl with C4; Fig. 1). The yield increased to 22 % (Table 2) when water/ethanol (9:1) was used as solvent but the reaction did not proceed in non-aqueous solvents. Lewis acid triflates (Sc, La, In, Yb) rapidly catalyzed the formation of imine (**5**) but resulted in no three-component products. At elevated temperatures, brown intractable mixtures were produced.

In terms of substrate scope, we found that the reaction required water as the primary solvent and that a small amount of ethanol improved the yield by reducing the precipitation of the intermediate imine. However, higher proportions of organic

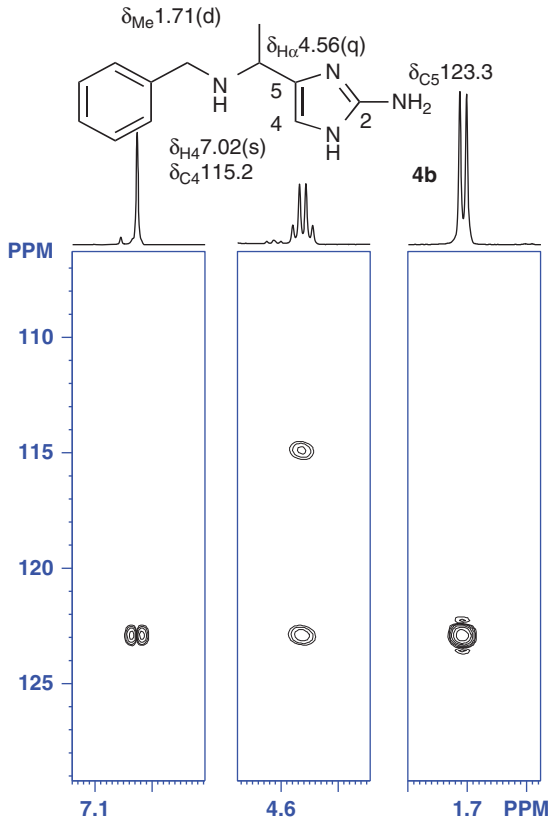


Fig. 1. Heteronuclear Multiple Bond Correlation (HMBC) spectrum of **4b** showing correlations between (a) H5 and C4 (123 ppm); (b) Hα and C5 and C4; and (c) the Cα-Me with C4.

Table 2. Three-component Mannich-like reaction of 2-aminoimidazole (2-AI) with different aldehydes and amines

R^A	R_1^A	Product	Yield of **4**[B] [%]	2-AI recovered [%]	Yield of **4** based on recovered 2-AI [%]
H	Benzyl	**4a**	20	56	45
Me	Benzyl	**4b**	22	64	61
Et	Benzyl	**4c**	15	61	38
	Butyl	**4d**	19	52	40
	Hexyl	**4e**	19	66	56
	Cyclohexyl	**4f**	13	56	30
Pr	Benzyl	**4g**	18	48	35
	Butyl	**4h**	23	74	88
	Hexyl	**4i**	15	68	47
	Cyclohexyl	**4j**	17	52	35

[A]R, R_1 as per Scheme 2.
[B] 2-AI with 2 equiv. Na_2CO_3, 2 equiv. aldehyde and 1 equiv. amine, stirred overnight in 10 % aqueous ethanol at room temperature.

solvent led to lower yields. Given the requirement for aqueous conditions, aromatic amines and aldehydes proved problematic owing to the insolubility of the intermediate imine.

Conclusion

Although this new reaction produced only moderate yields, it is reasonably general and can be run under mild and green conditions (Table 2). Notably though, aromatic aldehydes and

anilines did not yield the three-component products. This may be owing to solubility issues associated with the imine in aqueous mixtures.

There are several natural products bearing the 2-AI nucleus substituted at the 4-position. This three-component reaction of 2-AI will not only help provide access to these natural products but may also be useful in the generation of libraries of natural-product-like 2-AIs. The reaction is highly regiospecific and shows promise as a diversity-generating reaction, and is the first example of a three-component Mannich reaction of 2-AI. In addition, the reaction could also be directed to other pathways such as the Povarov reaction.[12] These studies are currently in progress.

Experimental

General Experimental Procedures

Chloroform, dichloromethane, ethanol and methanol were obtained from Froline (Australia). All other reagents were obtained from Aldrich (USA). Merck silica gel 60 (230–400 mesh) was used for column chromatography. NMR spectra were recorded in 5-mm 507-PP Pyrex tubes (Wilmad, USA) on either a DPX-400 400 MHz or DRX-600K 600 MHz spectrometer (Bruker, Germany). Chemical shifts of ^{1}H and ^{13}C NMR were referenced to the solvents peaks: δ_H 3.30 and δ_C 49.0 ppm for CD_3OD. High-resolution mass spectra (HRMS) were measured on Waters Q-TOF Ultima tandem quadrupole–time-of-flight instrument at the mass spectrometry laboratory, University of Illinois at Urbana–Champaign.

General Method for the Preparation of **4a–j**

2-AI hemisulfate (0.37 mmol) was stirred with sodium carbonate (0.75 mmol) in water/ethanol (9:1) at room temperature for 5 min. Amine (0.75 mmol) was added to the reaction mixture, followed by the dropwise addition of the aldehyde (0.75 mmol) over 5 min. After 10 min, a precipitate was formed but stirring was continued for an additional 8–12 h, after which the solvent was removed under reduced pressure to yield a brown solid, which was subjected to column chromatography over silica gel using a gradient of 5:95–15:85 (methanol/dichloromethane saturated with ammonia) to afford 4-substituted imidazoles **4** (13–23 %) and unreacted 2-AI (48–74 %). All the compounds were characterized and stored as their TFA salts.

*4-((Benzylamino)methyl)-1*H*-imidazol-2-amine* ***4a***

White solid. δ_H (400 MHz, CD_3OD) 7.42–7.50 (m, 5H), 6.97 (s, 1H), 4.25 (s, 2H), 4.22 (d, *J* 0.69, 2H). δ_C (100 MHz, CD_3OD) 149.8, 132.1, 131.0, 130.7, 130.3, 118.9, 116.5, 52.0, 41.5. *m/z* (HRMS) 203.1297 $[M + H]^+$; $C_{11}H_{15}N_4$ requires 203.1297.

*4-(1-(Benzylamino)ethyl)-1*H*-imidazol-2-amine* ***4b***

White solid. δ_H (400 MHz, CD_3OD) 7.39–7.47 (m, 5H), 7.02 (s, 1H), 4.56 (q, *J* 6.8, 1H), 4.17 (m, 2H), 1.71 (d, *J* 6.87, 3H). δ_C (100 MHz, CD_3OD) 150.0, 132.2, 130.9, 130.6, 130.2, 123.3, 115.2, 50.6, 50.4, 17.0. δ_N (60.8 MHz, CD_3OD) 134.0 (N3), 132.7 (N1), 59.7 (CH_2 –NH–CH). *m/z* (HRMS) 217.1452 $[M + H]^+$; $C_{12}H_{17}N_4$ requires 217.1453.

*4-(1-(Benzylamino)propyl)-1*H*-imidazol-2-amine* ***4c***

White solid. δ_H (400 MHz, CD_3OD) 7.52 (s, 5H), 7.03 (s, 1H), 4.26 (dd, *J* 11.0, 4.5, 1H), 4.14 (m, 2H), 1.95–2.16 (m, 2H), 0.92 (t, *J* 7.36, 3H). δ_C (100 MHz, CD_3OD) 150.2, 132.5, 130.9, 130.6, 130.2, 121.8, 116.3, 56.8, 50.8, 25.3, 10.3. *m/z* (HRMS) 231.1604 $[M + H]^+$; $C_{13}H_{19}N_4$ requires 231.1610.

*4-(1-(Butylamino)propyl)-1*H*-imidazol-2-amine* ***4d***

White solid. δ_H (400 MHz, CD_3OD) 7.03 (s, 1H), 4.21 (dd, *J* 10.9, 4.7, 1H), 2.84–3.01 (m, 2H), 1.93–2.13 (m, 2H), 1.57–1.73 (m, 2H), 1.34–1.44 (m, 2H), 0.93 (m, 6H). δ_C (100 MHz, CD_3OD) 150.2, 121.4, 116.5, 56.6, 46.8, 29.2, 25.2, 20.7, 13.7, 10.3. *m/z* (HRMS) 197.1770 $[M + H]^+$; $C_{10}H_{21}N_4$ requires 197.1766.

*4-(1-(Hexylamino)propyl)-1*H*-imidazol-2-amine* ***4e***

White solid. δ_H (400 MHz, CD_3OD) 7.03 (s, 1H), 4.21 (dd, *J* 10.8, 4.8, 1H), 3.00–2.85 (m, 2H), 2.11–1.95 (m, 2H), 1.73–1.59 (m, 2H), 1.41–1.26 (m, 6H), 0.92 (t, *J* 7.4, 3H), 0.89 (t, *J* 6.8, 1H). δ_C (100 MHz, CD_3OD) 150.3, 121.5, 116.4, 56.6, 47.1, 32.3, 27.2, 25.2, 23.3, 14.1, 10.4. *m/z* (HRMS) 225.2085 $[M + H]^+$; $C_{12}H_{25}N_4$ requires 225.2079.

*4-(1-(Cyclohexylamino)propyl)-1*H*-imidazol-2-amine* ***4f***

White solid. δ_H (400 MHz, CD_3OD) 7.05 (s, 1H), 4.36 (dd, *J* 10.9, 4.7, 1H), 3.04–2.94 (m, 1H), 2.21–2.14 (m, 1H), 2.07–1.93 (m, 3H), 1.89–1.79 (m, 2H), 1.72–1.64 (m, 1H), 1.44–1.14 (m, 5H), 0.91 (t, *J* 7.5, 3H). δ_C (100 MHz, CD_3OD) 151.4, 121.6, 116.3, 56.7, 53.3, 30.9, 29.8, 25.9, 25.5, 25.4, 25.3, 10.2. *m/z* (HRMS) 223.1925 $[M + H]^+$; $C_{12}H_{23}N_4$ requires 223.1923.

*4-(1-(Benzylamino)butyl)-1*H*-imidazol-2-amine* ***4g***

δ_H (400 MHz, CD_3OD) 7.38–7.46 (m, 5H), 7.04 (s, 1H), 4.37 (dd, *J* 9.3, 6.3, 1H), 4.15 (m, 2H), 1.96–2.07 (m, 2H), 1.24–1.35 (m, 2H), 0.95 (t, *J* 7.62, 3H). δ_C (100 MHz, CD_3OD) 150.2, 132.3, 130.9, 130.6, 130.2, 121.6, 116.4, 55.1, 50.6, 33.7, 20.0, 13.5. *m/z* (HRMS) 245.1769 $[M + H]^+$; $C_{14}H_{21}N_4$ requires 245.1766.

*4-(1-(Butylamino)butyl)-1*H*-imidazol-2-amine* ***4h***

White solid. δ_H (400 MHz, CD_3OD) 7.03 (s, 1H), 4.28 (dd, *J* 10.2, 5.3, 1H), 2.83–3.0 (m, 2H), 1.92–2.05 (m, 2H), 1.56–1.72 (m, 2H), 1.25–1.45 (m, 4H), 0.90–0.99 (m, 6H). δ_C (100 MHz, CD_3OD) 150.3, 121.8, 116.3, 55.0, 46.7, 33.7, 29.2, 20.7, 20.0, 13.7, 13.5. *m/z* (HRMS) 211.1931 $[M + H]^+$; $C_{11}H_{23}N_4$ requires 211.1923.

*4-(1-(Hexylamino)butyl)-1*H*-imidazol-2-amine* ***4i***

White solid. δ_H (400 MHz, CD_3OD) 7.03 (s, 1H), 4.29 (dd, *J* 10.1, 5.5, 1H), 3.00–2.83 (m, 2H), 2.03–1.92 (m, 2H), 1.73–1.59 (m, 2H), 1.39–1.24 (m, 8H), 0.95 (t, *J* 7.16, 3H), 0.89 (t, *J* 6.79, 3H). δ_C (100 MHz, CD_3OD) 150.3, 121.7, 116.4, 55.0, 47.0, 33.7, 32.3, 27.2, 23.3, 20.0, 14.1, 13.5. *m/z* (HRMS) 239.2242 $[M + H]^+$; $C_{13}H_{27}N_4$ requires 239.2236.

*4-(1-(Cyclohexylamino)butyl)-1*H*-imidazol-2-amine* ***4j***

White solid. δ_H (400 MHz, CD_3OD) 7.06 (s, 1H), 4.43 (dd, *J* 10.7, 5.0, 1H), 3.03–2.94 (m, 1H), 2.22–2.14 (m, 1H), 2.06–1.78 (m, 5H), 1.72–1.64 (m, 1H), 1.41–1.17 (m, 7H), 0.95 (t, *J* 7.39, 3H). δ_C (100 MHz, CD_3OD) 150.3, 121.7, 116.2, 56.6, 51.8, 34.1, 30.9, 29.8, 26.0, 25.4, 25.3, 19.9, 13.5. *m/z* (HRMS) 237.2078 $[M + H]^+$; $C_{13}H_{25}N_4$ requires 237.2079.

N-(2-Nitrobenzylidene)-1H-imidazol-2-amine ***5c***

Yellow solid. δ_H (400 MHz, CD_3OD) 9.38 (s, 1H), 8.29 (dd, *J* 7.7, 1.3, 1H), 8.05 (dd, J 8.0, 1.2, 1H), 7.77 (t, *J* 8.2, 1H), 7.70 (t, *J* 8.0, 1H), 7.07 (s, 2H). δ_C (100 MHz, CD_3OD) 154.3, 149.0, 131.9, 130.6, 128.7, 128.4, 127.6, 126.3, 123.1. *m*/*z* (HRMS) 217.0721 $[M + H]^+$; $C_{10}H_9N_4O_2$ requires 217.0720.

N-(3-Nitrobenzylidene)-1H-imidazol-2-amine ***5b***

Orange solid. δ_H (400 MHz, CD_3OD) 9.08 (s, 1H), 8.78 (s, 1H), 8.35–8.24 (m, 2H), 8.72 (t, *J* 8.9, 1H), 7.06 (s, 2H). δ_C (100 MHz, CD_3OD) 156.6, 147.7, 136.4, 133.3, 128.8, 124.4, 121.3. *m*/*z* (HRMS) 217.0723 $[M + H]^+$; $C_{10}H_9N_4O_2$ requires 217.0720.

N-Benzylidene-1H-imidazol-2-amine ***5a***

δ_H (400 MHz, CD_3OD) 9.00 (s, 1H), 7.94 (dd, *J* 7.91, 1.59, 2H), 7.55–7.42 (m, 3H), 7.07 (s, 2H). δ_C (100 MHz, CD_3OD) 159.6, 149.8, 134.6, 130.6, 127.5, 127.4. *m*/*z* (HRMS) 172.0870 $[M + H]^+$; $C_{10}H_{10}N_3$ requires 172.0869.

Accessory Publication

^1H and ^{13}C NMR spectra for all compounds are available on the Journal's website.

Acknowledgements

The authors thank Macquarie University for financial support. SRS is the grateful recipient of a Macquarie-funded international PhD scholarship (iMURS).

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