Tetrahedron xxx (2014) 1–6

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Exploring the synthetic utility of 1-alkynylimidazoles: regiocontrolled cyclization to diverse imidazoazines and imidazoazoles

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ARTICLE INFO

Article history:
Received 3 April 2014
Received in revised form 28 April 2014
Accepted 30 April 2014
Available online xxx

ABSTRACT

Regiocontrolled cyclizations involving alkynes have utility in the formation of diverse heterocyclic systems. Here we report the participation of model 1-alkynylimidazoles in intramolecular hydroalkoxylation and hydroamination reactions leading to diverse imidazoazine and imidazoazole ring systems. In many cases, the preference for 5-*exo*-*dig* or 6-*endo*-*dig* cyclization can be controlled by variations in reaction conditions. This work establishes 1-alkynylimidazoles as versatile intermediates in the synthesis of a wide variety of fused-imidazole heterocycles.

1. Introduction

N-Fused heterocycles incorporating an imidazole ring are versatile chemo-types for both drug discovery and chemical biology.[1,2] These *N*-fused-imidazole heterocycles appear as cores of natural products, such as nagstatin[3] and cypridine luciferin[4] (Fig. 1), as well as in many pharmaceutical agents, such as the hypnotic zolpidem,[5] the kinase inhibitor SKF 86002,[6] and others[7] (Fig. 1). Paradoxically, despite the demonstrated biological activity associated with these fused-imidazole heterocycles, certain members of this class are virtually unexplored, such as the 1*H*,3*H*-imidazo[1,5-*c*]oxazole system[8] (Fig. 1). Thus, the development of new synthetic routes to these heterocycles may both aid the preparation of well-established core structures and provide entry to the still unexplored regions of this biologically promising chemical space. As such, this remains a very active area of research.[9–15]

The synthesis of imidazole-fused heterocycles generally involves one of two strategies: elaboration of the imidazole cycle starting from a functionalized heterocycle, or formation of the fused-heterocycle via the cyclization of an imidazole derivative.[9,11] While both strategies offer advantages and limitations, the later approach has the potential to afford a wide range of imidazole-fused heterocycles from a common imidazole intermediate.

Recently, copper-catalyzed coupling reactions between imidazoles and bromoalkynes or their surrogates have emerged as a direct, convenient, and efficient route to 1-alkynylimidazoles.[16–19] We reasoned that these 1-alkynylimidazoles could in turn serve as versatile intermediates in the preparation of a wide range of imidazole-fused heterocycles through cyclizations involving the 1-alkynyl substituent.[20] One important consideration in this approach is the ability to control the regiochemistry of these cyclizations. We have previously shown that 1-alkynylimidazoles bearing a carbinol substituent at the 2-position undergo regiocontrolled intramolecular hydroalkoxylation.[21] Under base-catalysis, 1-alkynyl-2-hydroxymethylimidazoles, such as **1** undergo selective 5-*exo*-*dig* cyclization to afford 5,7-dihydro-5-methyleneimidazo[1,2-*c*]oxazoles **2** (Scheme 1). In contrast, under Au-catalysis **1** undergoes exclusive 6-*endo*-*dig* cyclization to afford 8*H*-imidazo[2,1-*c*][1,4]oxazines **3** (Scheme 1).

Here we describe studies that examine the generality of this regiocontrol in the intramolecular hydroalkoxylation and hydroamination reactions of model 1-alkynylimidazoles. In addition, a range of regiospecific alternative cyclizations of 2-carboxaldehyde substituted 1-alkynylimidazoles are also described. Overall, these studies demonstrate the synthetic versatility of 1-alkynylimidazoles in the rapid and regiocontrolled preparation of a wide range of well-established and novel bicyclic imidazole heterocycles.

2. Results and discussion

We first examined if the reagent-controlled regioselective hydroalkoxylation cyclization of 2-substituted 1-alkynylimidazoles (Scheme 1) also holds when the carbinol moiety is located at 5-position of the 1-alkynylimidazole. In order to access the required carbinol, we employed the sequential metalation–functionalization of the 4-phenyl-substituted 1-alkynylimidazole **4** (Scheme 2). In one

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http://dx.doi.org/10.1016/j.tet.2014.04.099

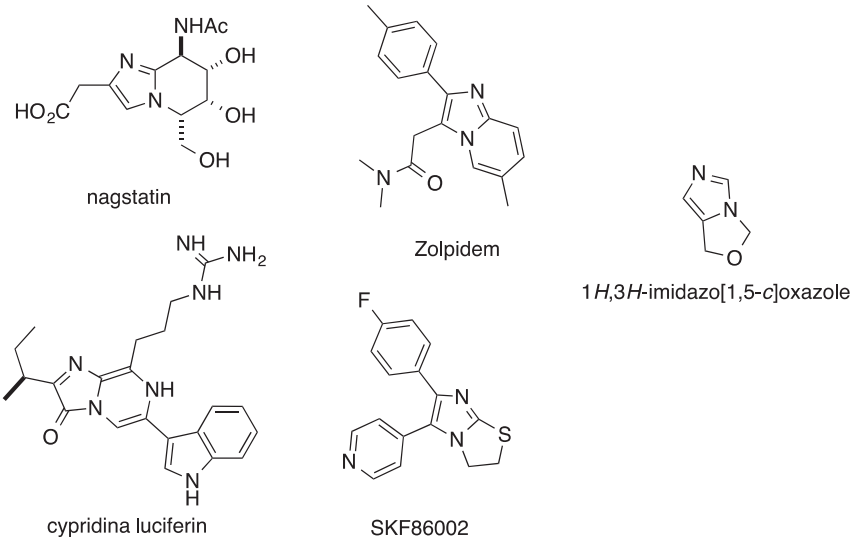
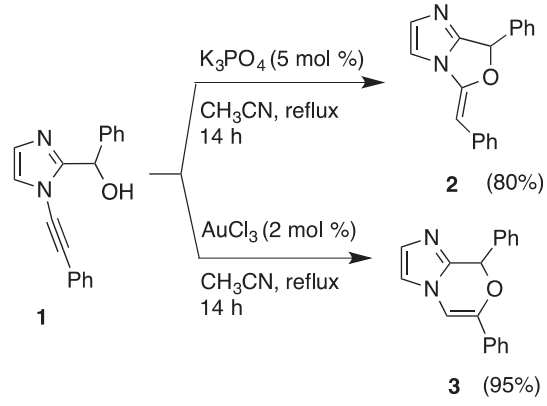
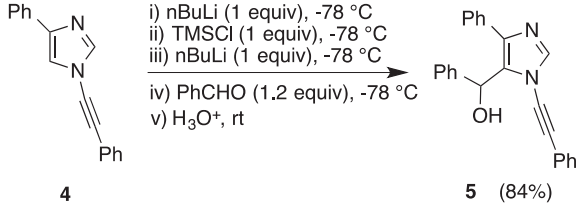


Fig. 1. Examples of *N*-fused-imidazole heterocycles.



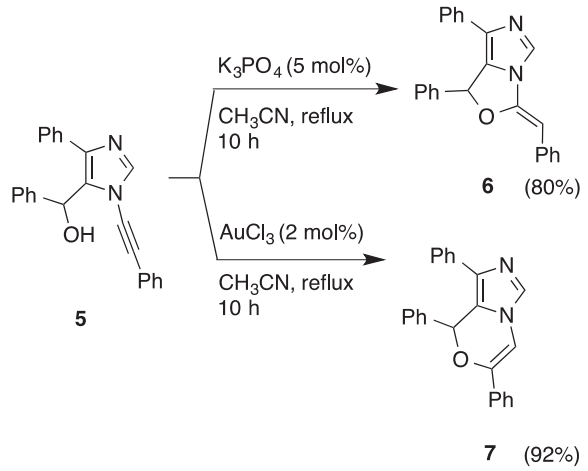
Scheme 1. Reagent-controlled regioselective hydroalkoxylation cyclization of 2-carbinol substituted 1-alkynylimidazoles.[21]



Scheme 2. Preparation of 5-carbinol-functionalized 1-alkynylimidazole.

pot, 1-alkynylimidazole **4** was deprotonated with *n*-BuLi at −78 °C to afford the 2-lithio species,[20] which was trapped with trimethylsilyl chloride. A second addition of base followed by trapping of the resulting 5-lithio species with benzaldehyde afforded the desired carbinol **5** in good yield after acidic work-up (Scheme 2).

Treating 1-alkynylimidazole **5** under the same conditions as employed for the regioselective 5-*exo*-*dig* cyclization of **1** (5 mol % K_3PO_4 in CH_3CN under reflux) afforded the 5-*exo*-*dig* cyclization product **6** in 80% yield after chromatography (Scheme 3). In contrast, treatment of **5** with 2 mol % $AuCl_3$ afforded exclusively the 6-*endo*-*dig* cyclization product **7**, which was isolated in 92% yield after chromatography (Scheme 3). The structures of **6** and **7** were assigned based on their ^1H and ^{13}C NMR spectra in comparison with that of **2** and **3**, respectively. Thus, the reagent-controlled regioselective cyclization of 5-substituted 1-alkynylimidazole **5** mirrors that of the 2-substituted isomer **1**. This indicates that the subtle



Scheme 3. Regiocontrolled cyclization of 5-carbinol-functionalized 1-alkynylimidazole **5**.

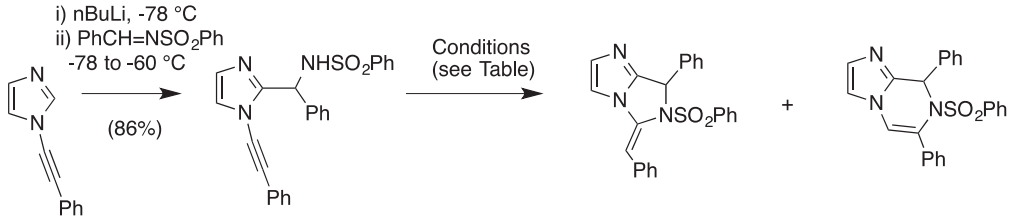
changes in geometry of the attacking hydroxyl group and the 1-alkynyl between isomers **1** and **5** do not affect the origin or magnitude of the reagent-controlled regioselectivity.

We next explored the regioselectivity of the intramolecular hydroamination reactions of 1-alkynylimidazoles. We prepared the precursor 2-substituted sulfonamide by deprotonation of the 1-alkynylimidazole **8**[16] followed by addition of (*E*)-benzylidene-benzenesulfonamide to afford sulfonamide **9** in 86% yield. Compound **9** was then subjected to various cyclization conditions (Table 1).

Cyclization of **9** did not occur in the presence of $AuCl_3$ even with prolonged reaction times and only starting material was recovered (Table 1, entry 1). This was somewhat surprising in light of the results shown in Schemes 1 and 3, but may be due to preferential coordination of the Au species with the sulfonamide moiety of **9**. Under base catalysis with K_3PO_4 at room temperature, the desired products were obtained as a 1:1 mixture of chromatographically separable 5-*exo*-*dig* and 6-*endo*-*dig* products (Table 1, entry 2). The structure of the 6-*endo*-*dig* cyclization product **11** was confirmed by single crystal X-ray analysis (see Supplementary data), while that of the 5-*exo*-*dig* cyclization product **10** was assigned in analogy to the 5-*exo*-*dig* cyclization product **2**, which was also determined by single crystal X-ray analysis.[21] While the lack of regiocontrol under these conditions was disappointing, the ratio **10**/**11** was highly dependent on the reaction temperature, ranging from 5:1 at 5 °C in CH_3CN (Table 1, entry 3) to 1:2 at reflux (Table 1, entry 4).

Please cite this article in press as: Laroche, C.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.04.099

Table 1
Regiocontrolled intramolecular hydroamination of 1-alkynylimidazole **9**



8 **9** **10** **11**

Entry	Conditions	Combined yield[a] (%)	Ratio (**10**/**11**)	Purified yield (Compound)[b]
1	$AuCl_3$ (2mol %) CH_3CN reflux	0	—	*na*[c]
2	K_3PO_4 (5 mol %) CH_3CN at rt	90	5:1	75% (**10**)
3	K_3PO_4 (5 mol %) CH_3CN at 5 °C	90	1:1	*nd*[d]
4	K_3PO_4 (5 mol %) CH_3CN at reflux	90	1:2	60% (**11**)

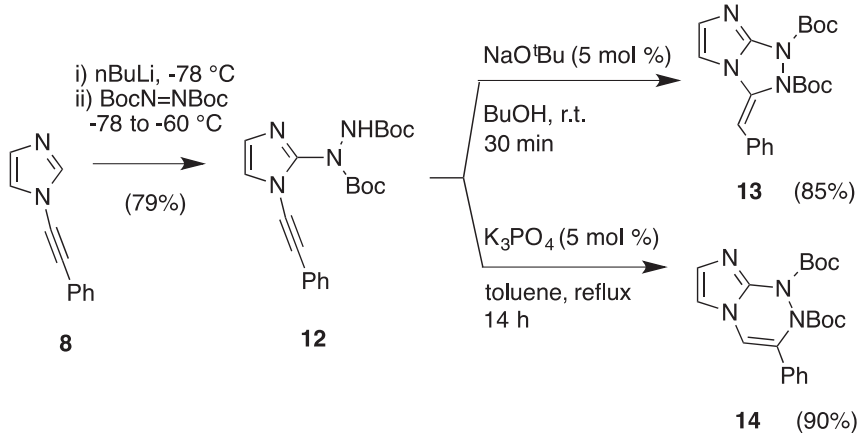
[a] Combined yield of **10** and **11**.
[b] Purified yield of major isomer.
[c] Not applicable.
[d] Not determined.

Interestingly, this reaction temperature-dependent regioselectivity does not appear to simply reflect kinetic versus thermodynamic control, as re-subjecting purified **10** or **11** to the reaction conditions did not afford the expected mixture of isomers. Still, synthetically useful yields of either isomer could be obtained (Table 1, entries 2 and 4). Other attempts to enhance the cyclization mode selectivity by using higher boiling point solvent (toluene) and other transition metals (Pd, Ag, Cu) have been explored with no success.

We next explored the scope of this intramolecular hydroamination route to other fused imidazole systems. Deprotonation of **8** followed by trapping with di-(*tert*-butyl)azodicarboxylate afforded the hydrazine **12** in 79% yield (Scheme 4). Compound **12** was then subjected to cyclization in the presence of K_3PO_4 (5 mol %) in CH_3CN at various temperatures. The reaction did not proceed at 5 °C nor at room temperature. In acetonitrile at reflux, the expected products were obtained in 95% combined yield as a 1:4 mixture of the 5-*exo*-*dig* cyclization product **12** and the 6-*endo*-*dig* product **13**. By increasing the temperature ever further by running the reaction in toluene under reflux, a 90% yield of the pure 6-*endo*-*dig* cyclization product **13** could be obtained (Scheme 4). We reasoned that the inability to obtain reaction products at temperatures lower than refluxing acetonitrile might be due to the higher pK_a of **11** compared to the sulfonamide **8**. Upon performing the cyclization reaction of **11** with catalytic NaO^{t}Bu in ^{t}BuOH at 5 °C, the expected products **12** and **13** were obtained in 92% combined yield as a 12:1 mixture, affording chromatographically isolated 5-*exo*-*dig* product **12** in 85% yield (Scheme 4).

Finally, we explored the use of 2-carbaldehyde 1-alkynylimidazoles as precursors to a variety of imidazo-fused heterocycles. The aldehyde **15**, prepared from **8** by deprotonation and trapping with DMF,[21] undergoes cyclization to the imidazolopyrazine **16** when treated with ammonia in MeOH/THF in the presence of catalytic $Cu(OTf)_2$ (Scheme 5). Similarly, in the presence of catalytic $Cu(OTf)_2$ in ethanol, **15** is cleanly converted to the cyclic acetal **17**. Aldehyde **15** undergoes cyclization in the absence of metal catalyst when treated with hydroxylamine hydrochloride in DMF to afford the imidazolopyrazine *N*-oxide **18**. No products of 5-*exo*-*dig* cyclization were observed in any of these cyclizations. Thus, under the influence of catalytic Cu^{2+} (i.e., **15**→**16** and **15**→**17**) or when the nucleophilic group involved in the cyclization is an sp^2-nitrogen (i.e., **15**→**18**), only products of 6-*endo*-*dig* cyclization are observed.

In conclusion, we have shown that 1-alkynylimidazole derivatives represent versatile building blocks for the construction of an array of *N*-fused-imidazole heterocycles. The regiocontrol of both intramolecular hydroalkoxylation and hydroamination reactions can be accomplished simply through reagent- or temperature-control, affording synthetically useful yields of either products of 5-*exo*-*dig* or 6-*endo*-*dig* cyclization. In contrast,



8 **12**

Scheme 4. Regiocontrolled cyclization of 2-hydrazinyl-functionalized 1-alkynylimidazole.

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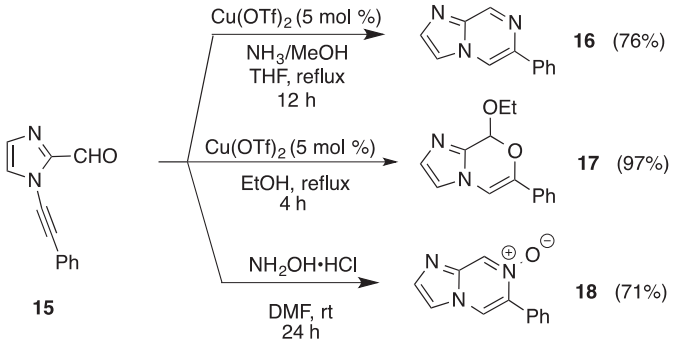

Scheme 5. Exclusive 6-*endo-dig* cyclizations of 2-carbaldehyde-functionalized 1-alkynylimidazole.

exclusive 6-*endo-dig* cyclization is observed for 2-carboxaldehyde-substituted 1-alkynylimidazole **14**, providing rapid access to known and novel imidazole heterocycles.

3. Experimental section

3.1. General

All reactions were performed under an atmosphere of argon in either oven- or flame-dried glassware. Immediately prior to use, THF was distilled from Na/benzophenone, whereas CH_3CN and toluene were distilled from CaH_2. Ethanol and DMF were dried over 4 Å molecular sieves. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Flash chromatography was performed with EM Reagent silica gel (230–400 mesh) using the mobile phase indicated. Melting points (open capillary) are uncorrected. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ on a spectrometer operating at 400 and 100 MHz, respectively, except where noted, and are reported in parts per million using solvent as internal standard. All mass spectra were obtained in the positive mode by CI using methane as the ionizing gas.

*3.1.1. Phenyl(4-phenyl-1-(2-phenylethynyl)-1H-imidazol-5-yl)methanol (**5**).* A stirred solution of 4-phenyl-1-(2-phenylethynyl)-1*H*-imidazole (**4**)[16] (324 mg, 1.32 mmol) in 20 mL of THF was cooled to −78 °C. The following successive additions to the reaction solution were carried out while maintaining the reaction temperature at −78 °C. *n*-BuLi (2 M in hexanes, 0.66 mL, 1.32 mmol) was added by syringe and the reaction stirred for 20 min. TMSCl (0.17 mL, 1.327 mmol) was added by syringe and the reaction stirred for 45 min. A second equivalent of *n*-BuLi (2 M in hexanes, 0.66 mL, 1.32 mmol) was added and the reaction stirred for 30 min. Benzaldehyde (0.162 mL, 1.592 mmol) was added by syringe and the reaction allowed to stir for 30 min. Aqueous 1 M HCl (10 mL) was added by syringe and the reaction was allowed to reach room temperature. The reaction mixture was extracted with EtOAc (3×20 mL). The combined organic extracts were dried over Na_2SO_4, and the solvents were removed by reduced pressure giving a light yellow oil, which was purified by flash chromatography (0–5% EtOAc in hexanes). Purification afforded 390 mg (84%) of phenyl(4-phenyl-1-(2-phenylethynyl)-1*H*-imidazol-5-yl)methanol (**5**) as a white crystalline solid. R_f 0.6 (25% EtOAc in hexane); Mp 155–157 °C; ^{1}H NMR δ 7.80 (1H, s), 7.67–7.61 (2H, m), 7.46–7.25 (11H, m), 7.19–7.14 (2H, m), 6.36 (1H, s), 3.15 (1H, s, O*H*); ^{13}C NMR δ 140.7, 140.4, 133.1, 131.3 (2C), 130.2, 128.8, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.1 (2C), 127.8, 127.5, 126.0 (2C), 120.9, 77.2, 73.7, 66.5; IR (KBr) 3172, 1741, 1597, 1410, 1236, 1204, 1038, 962, 770; MS 351 (M+1, 100%), 333 (M−18, 76%); HRMS calcd for $C_{24}H_{19}N_2O$ (M+H$^+$) 351.1497, found 351.1495.

*3.1.2. (Z)-3-Benzylidene-1,3-dihydro-1,7-diphenylimidazo[1,5-c]oxazole (**6**).* A round bottom flask was charged with K_3PO_4 (3 mg, 0.014 mmol). To this was added, by syringe, a solution of phenyl(4-phenyl-1-(2-phenylethynyl)-1*H*-imidazol-5-yl)methanol (**5**) (100 mg, 0.285 mmol) in 10 mL of CH_3CN. The reaction was held at reflux for 10 h, cooled to room temperature, diluted with 10 mL H_2O, and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding a light yellow oil, which was purified by flash chromatography (0–6% EtOAc in hexanes). Purification afforded (*Z*)-3-benzylidene-1,3-dihydro-1,7-diphenylimidazo[1,5-*c*]oxazole (**6**) (86 mg, 87%) as a white crystalline solid. R_f 0.44 (10% EtOAc in hexane); Mp 190–191 °C; ^{1}H NMR δ 7.94 (1H, s), 7.54–7.39 (9H, m), 7.32–7.13 (6H, m), 6.71 (1H, s), 5.63 (1H, s); ^{13}C NMR δ 142.8, 135.3, 133.7, 133.2, 132.4, 130.1, 129.2 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 128.2, 127.3 (2C), 127.0, 126.0, 125.8, 125.5 (2C), 85.37, 82.37; IR (KBr) 1702, 1598, 1462, 1418, 1268, 1152, 1054, 950, 696 cm^{-1}; MS 351 (M+1, 100%), 119 (M−232, 39%), 233 (M−118, 38%), 352 (M+2, 34%); HRMS calcd for $C_{24}H_{19}N_2O$ (M+H$^+$) 351.1497, found 351.1496.

*3.1.3. 1,6,8-Triphenyl-8H-imidazo[5,1-c][1,4]oxazine (**7**).* To a round bottom flask was added by syringe a solution of $AuCl_3$ (0.6 mL of 0.01 M in CH_3CN, 0.006 mmol) followed by the addition of a solution of phenyl(4-phenyl-1-(2-phenylethynyl)-1*H*-imidazol-5-yl) methanol (**5**) (101 mg, 0.29 mmol) in 10 mL of CH_3CN and the resulting solution was degassed by sparging with argon. The reaction was heated under reflux for 10 h, cooled to room temperature, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding a light yellow oil, which was purified by flash chromatography (0–2% EtOAc in hexanes). Purification afforded 1,6,8-triphenyl-8*H*-imidazo[5,1-*c*][1,4] oxazine (**7**) (92 mg, 91%) as a white crystalline solid. R_f 0.53 (10% EtOAc in hexane); Mp 142–143 °C; ^{1}H NMR δ 7.78 (1H, s), 7.6–7.51 (4H, m), 7.37–7.22 (11H, m), 7.10 (1H, s), 6.83 (1H, s); ^{13}C NMR δ 141.7, 137.5, 136.3, 133.8, 132.9, 132.5, 129.1, 129.0, 128.7 (2C), 128.6 (2C), 128.5 (2C), 127.7 (2C), 126.9, 126.2 (2C), 124.4 (2C), 118.2, 101.5, 74.2; IR (KBr) 1683, 1615, 1492, 1457, 1402, 1285, 1219, 743, 691 cm^{-1}; MS 351 (M+1, 100%), 352 (M+2, 19%), 350 (M, 5%) 245 (M−105, 4%); HRMS calcd for $C_{24}H_{19}N_2O$ (M+H$^+$) 351.1497, found 351.1497.

*3.1.4. N-(Phenyl(1-(phenylethynyl)-1H-imidazol-2-yl)methyl)benzenesulfonamide (**9**).* A round bottom flask was charged with 1-(phenylethynyl)-1*H*-imidazole (**8**)[16] (84 mg, 0.5 mmol). The solution was brought to −78 °C and *n*-BuLi (0.2 mL, 0.5 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min followed by the addition of *N*-benzylidenebenzenesulfonamide (123 mg, 0.5 mmol). The reaction was allowed to reach −60 °C then quenched with 1 M HCl (2 mL), diluted with 10 mL H_2O, and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated by reduced pressure yielding a white solid that was purified by flash chromatography (50% EtOAc in hexanes). Purification afforded (**9**) (178 mg, 86%) as a white solid. R_f 0.2 (50% EtOAc in hexane); Mp 177–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.62 (2H, m), 7.44–7.36 (6H, m), 7.32–7.24 (2H, m), 7.24–7.18 (5H, m), 6.95 (1H, d, *J*=1.5 Hz), 6.88 (1H, d, *J*=1.5 Hz), 6.43 (1H, br s, N*H*), 5.95 (1H, d, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 140.1, 137.2, 132.1, 131.6 (2C), 129.2, 128.6 (2C), 128.6 (4C), 128.3, 128.2, 127.4 (2C), 126.8 (2C), 121.6, 120.5, 76.5, 74.2, 53.7; IR (KBr) 3061, 2868, 2257, 1481, 1428, 1333, 1169,

1090, 1063, 948 cm^{-1}; MS 827 (2M+1, 4%), 414 (M+1, 100%); HRMS calcd for $C_{24}H_{20}N_3O_2S$ ($M+H^+$) 414.1276, found 414.1282.

*3.1.5. (E)-5-Benzylidene-6-(phenylsulfonyl)-7-phenyl-6,8-dihydro-5H-imidazo[1,5-a]imidazole (**10**).* A two-neck round bottom flask was charged with *N*-(phenyl(1-(phenylethynyl)-1*H*-imidazol-2-yl) methyl)benzenesulfonamide (**9**) (103 mg, 0.25 mmol). To this was added, by syringe, CH_3CN (10 mL). The solution was brought to 0 °C, then K_3PO_4 (2.65 mg, 0.0125 mmol) was added. The reaction was held at 0 °C for 10 h then at 4 °C for 24 h, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding an orange solid that was purified by flash chromatography (50% EtOAc in hexanes). Purification afforded (*E*)-5-benzylidene-6-(phenylsulfonyl)-7-phenyl-6,8-dihydro-5*H*-imidazo[1,5-*a*]imidazole (**10**) (77 mg, 75%) as an orange solid. R_f 0.2 (40% EtOAc in hexane); Mp 154–156 °C; ^1H NMR δ 7.78–7.74 (2H, m), 7.69–7.65 (2H, m), 7.57–7.46 (3H, m), 7.44–7.32 (7H, m), 7.29–7.24 (1H, m), 6.98 (1H, d, J=1.4 Hz), 6.94 (1H, d, J=1.4 Hz), 6.32 (1H, s), 6.04 (1H, s); ^{13}C NMR δ 149.84, 135.7, 135.4, 135.2, 134.1, 132.8, 130.4, 129.2 (4C), 129.0 (2C), 128.7, 128.2 (2C), 128.0, 127.5 (2C), 126.8 (2C), 110.2, 107.6, 63.4; IR (KBr) 3155, 1673, 1541, 1472, 1449, 1413, 1396, 1285, 1170, 1093, 986 cm^{-1}; MS 414 (M+1, 100%); HRMS calcd for $C_{24}H_{20}N_3O_2S$ ($M+H^+$) 414.1276, found 414.1274. Elem. Anal. Calcd for $C_{24}H_{20}N_3O_2S$: C, 69.71; H, 4.63; N, 10.16. Found: C, 69.39; H, 4.63; N, 10.07.

*3.1.6. 6,8-Diphenyl-7-(phenylsulfonyl)-7,8-dihydroimidazo[1,2-a] pyrazine (**11**).* A two-neck round bottom flask was charged with *N*-(phenyl(1-(phenylethynyl)-1*H*-imidazol-2-yl)methyl)benzenesulfonamide (**9**) (103 mg, 0.25 mmol). To this was added, by syringe, CH_3CN (10 mL) then K_3PO_4 (2.65 mg, 0.0125 mmol). The reaction was heated under reflux for 1 h, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding a light yellow solid, which was purified by flash chromatography (50% EtOAc in hexanes). Purification afforded 6,8-diphenyl-7-(phenylsulfonyl)-7,8-dihydroimidazo[1,2-*a*]pyrazine (**11**) (62 mg, 60%) as a white crystalline solid. R_f 0.17 (40% EtOAc in hexane); Mp 153–155 °C; ^1H NMR δ 7.59–7.55 (2H, m), 7.46–7.38 (3H, m), 7.37–7.27 (8H, m), 7.17–7.12 (2H, m), 6.93 (1H, d, J=1.5 Hz), 6.82 (1H, s), 6.78 (1H, s), 6.62 (1H, d, J=1.5 Hz); ^{13}C NMR δ 140.8, 136.3, 135.9, 134.9, 133.0, 129.4, 129.0, 128.6 (2C), 128.5, 128.4 (4C), 127.8, 127.2 (2C), 127.1 (2C), 126.5 (2C), 116.2, 115.1, 57.4; IR (KBr) 3067, 1491, 1450, 1433, 1360, 1172, 1089, 980 cm^{-1}; MS 414 (M+1, 100%); HRMS calcd for $C_{24}H_{20}N_3O_2S$ ($M+H^+$) 414.1276, found 414.1276.

*3.1.7. Di-tert-butyl 1-(1-(phenylethynyl)-1H-imidazol-2-yl)hydrazine-1,2-dicarboxylate (**12**).* A round bottom flask was charged with 1-(phenylethynyl)-1*H*-imidazole (**8**)[16] (840 mg, 5 mmol). To this was added, by syringe, THF (30 mL). The solution was brought to −78 °C and *n*-BuLi (2.0 mL, 5 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min followed by the addition of di-(*tert*-butyl)azodicarboxylate (1.26 g, 5.5 mmol). The reaction mixture was stirred at −78 °C for 1 h then quenched with 1 M HCl (10 mL), and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding a white solid that was purified by flash chromatography (20% EtOAc in hexanes). Purification afforded di-*tert*-butyl 1-(1-(phenylethynyl)-1*H*-imidazol-2-yl)hydrazine-1,2-dicarboxylate (**12**) (1.51 g 76%) as a white solid. R_f 0.2 (20% EtOAc in hexane); Mp 72–75 °C; ^1H NMR δ 7.54–7.48 (3H, m), 7.37–7.33 (3H, m), 7.09 (1H, d, J=1.7 Hz), 6.97 (1H, d, J=1.7 Hz), 1.46 (18H, s); ^{13}C NMR δ 154.4, 152.4, 144.4, 131.5 (2C), 128.7, 128.3 (2C), 126.9, 121.3, 121.1, 83.5, 81.4, 28.1, 27.8; IR (KBr) 3179, 2979, 2265, 1737, 1553, 1441, 1394, 1325, 1248, 1153, 1081, 757 cm^{-1}; MS 399 (M+1, 100%); HRMS calcd for $C_{21}H_{27}N_4O_4$ ($M+H^+$) 399.2032, found 399.2035.

*3.1.8. (Z)-Di-tert-butyl 3-benzylidene-1H-imidazo[2,1-c][1,2,4]triazole-1,2(3H)-dicarboxylate (**13**).* Di-*tert*-butyl 1-(1-(phenylethynyl)-1*H*-imidazol-2-yl)hydrazine-1,2-dicarboxylate (**12**) (79.7 mg, 0.2 mmol) was dissolved in *t*-BuOH. To this solution was added NaO^tBu (1 mg, 0.01 mmol) and the reaction stirred at room temperature for 30 min. The reaction was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding a white solid that was purified by flash chromatography (50% EtOAc in hexanes). Purification afforded (*Z*)-di-*tert*-butyl 3-benzylidene-1*H*-imidazo[2,1-*c*][1,2,4]triazole-1,2(3*H*)-dicarboxylate (**13**) (68 mg, 85%) as a white solid. R_f 0.25 (50% EtOAc in hexane); Mp 150–153 °C; ^1H NMR δ 7.50–7.46 (2H, m), 7.33–7.27 (2H, m), 7.23–7.17 (1H, m), 7.04 (1H, d, J=1.6 Hz), 6.99 (1H, d, J=1.6 Hz), 6.02 (1H, s), 1.62 (9H, s), 1.25 (9H, s); ^{13}C NMR δ 151.2, 149.7, 145.8, 134.0, 133.9, 130.3, 128.2, 128.1, 127.1, 108.3, 99.9, 84.9, 84.8, 29.9 (3C), 27.4 (2C); IR (KBr) 1775, 1751, 1689, 1579, 1446, 1396, 1372, 1301, 1138, 969, 836, 754 cm^{-1}; MS 399 (M+1, 44%), 199 (M−199, 46%), 243 (M−155, 34%); HRMS calcd for $C_{21}H_{27}N_4O_4$ ($M+H^+$) 399.2032, found 399.2032.

*3.1.9. Di-tert-butyl 3-phenylimidazo[2,1-c][1,2,4]triazine-1,2-dicarboxylate (**14**).* A two-neck, round bottom flask was charged with di-*tert*-butyl 1-(1-(phenylethynyl)-1*H*-imidazol-2-yl)hydrazine-1,2-dicarboxylate (**12**) (20 mg, 0.05 mmol). To this was added, by syringe, toluene (10 mL) then K_3PO_4 (0.053 mg, 0.0025 mmol). The solution was held at reflux for 14 h then diluted with 5 mL H_2O and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding a white solid that was purified by flash chromatography (50% EtOAc in hexanes). Purification afforded di-*tert*-butyl 3-phenylimidazo[2,1-*c*][1,2,4]triazine-1,2-dicarboxylate (**14**) (18 mg, 90%) as a white solid. R_f 0.2 (50% EtOAc in hexane); Mp 202–205 °C; ^1H NMR δ 7.65–7.62 (2H, m), 7.43–7.33 (3H, m), 7.02 (1H, d, J=1.6 Hz), 6.99 (1H, d, J=1.6 Hz), 6.92 (1H, s), 1.58 (9H, s), 1.25 (9H, s); ^{13}C NMR δ 151.5, 151.1, 139.8, 133.4, 131.2, 128.7, 128.6, 127.8, 125.4, 113.7, 111.8, 84.0, 83.3, 28.0, 27.6; IR (KBr) 3133, 2979, 1738, 1550, 1495, 1433, 1370, 1305, 1153, 1120, 840, 757 cm^{-1}; MS 399 (M+1, 100%); HRMS calcd for $C_{21}H_{27}N_4O_4$ ($M+H^+$) 399.2032, found 399.2032.

*3.1.10. 6-Phenylimidazo[1,2-a]pyrazine (**16**).* A round bottom flask was charged with $Cu(OTf)_2$ (14 mg, 0.038 mmol) to which a solution of 1-(2-phenylethynyl)-1*H*-imidazole-2-carbaldehyde (**15**)[21] (150 mg, 0.765 mmol) in 10 mL THF was added by syringe followed by the addition of a 2 M solution of ammonia in methanol (0.42 mL, 0.842 mmol). The mixture was heated under reflux for 12 h, allowed to cool to room temperature, diluted with H_2O (10 mL), and extracted with EtOAc (3×20 mL). The organic extracts were combined, dried over Na_2SO_4, and the solvents removed under reduced pressure. The residual yellow oil was purified by flash chromatography (0–25% EtOAc in hexanes) to afford 6-phenylimidazo[1,2-*a*]pyrazine (**16**) (114 mg, 76%) as a colorless crystalline solid. R_f 0.32 (75% EtOAc in hexane); Mp=107–108 °C; ^1H NMR δ 9.12 (1H, d, J=1.6 Hz), 8.38 (1H, d, J=1.6 Hz), 7.87–7.84 (2H, m), 7.75 (1H, s), 7.67 (1H, s), 7.44–7.34 (3H, m); ^{13}C NMR δ 143.2, 140.0, 139.8, 136.3, 136.0, 129.0 (2C), 128.8, 126.3 (2C), 115.0, 113.9; IR (KBr) 1521, 1485, 1459, 1439, 1325, 1317, 1144, 917, 778, 691; MS 196 (M+1, 100%), 195 (M, 12%), 194 (M−1, 1%); HRMS calcd for $C_{12}H_{10}N_3$ ($M+H^+$) 196.0875, found 196.0878.

*3.1.11. 8-Ethoxy-6-phenyl-8H-imidazo[2,1-c][1,4]oxazine (**17**).* A round bottom flask was charged with $Cu(OTf)_2$ (9 mg, 0.025 mmol) to which 1-(2-phenylethynyl)-1*H*-imidazole-2-carbaldehyde (**15**)[21]

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(100 mg, 0.51 mmol) in ethanol (10 mL) was added by syringe. The reaction was held at reflux for 4 h then allowed to cool to room temperature. H_2O (10 mL) was added, the mixture extracted with CH_2Cl_2 (3×15 mL), the organic extracts were combined and dried over Na_2SO_4, and the solvents removed under reduced pressure. The residual yellow oil was purified by flash chromatography (0–25% EtOAc in hexanes) to afford 8-ethoxy-6-phenyl-8*H*-imidazo[2,1-*c*][1,4]oxazine (**17**) (120 mg, 97%) as a white crystalline solid. R_f 0.51 (25% EtOAc in hexane); Mp=86–87 °C; ^{1}H NMR δ 7.63–7.61 (2H, m), 7.41–7.34 (3H, m), 7.14 (1H, d, J=1.1 Hz), 7.09 (1H, s), 7.02 (1H, d, J=1.3 Hz), 6.36 (1H, s), 4.05 (1H, quint, J=11.9, 9.4 Hz), 3.87 (1H, quint, J=11.9, 9.4 Hz), 1.25 (3H, t, J=7.1 Hz); ^{13}C NMR δ 141.0, 137.4, 132.3, 129.6, 129.0, 128.7 (2C), 124.4 (2C), 115.4, 102.0, 94.6, 64.4, 15.2; IR (KBr) 3410, 3121, 2990, 2446, 1684, 1497, 1454, 1308, 1202, 1088, 1018, 970; MS 243 (M+1, 100%), 197 (M−46, 38%), 165 (M−78, 23%); HRMS calcd for $C_{14}H_{15}N_2O_2$ (M+H$^+$) 243.1134, found 243.1137.

*3.1.12. 6-Phenylimidazo[1,2-a]pyrazine 7-oxide (**18**).* A two-neck round bottom flask was charged with 1-(2-phenylethynyl)-1*H*-imidazole-2-carbaldehyde (**15**)[21] (50 mg, 0.25 mmol) to which was added by syringe DMF (10 mL) then hydroxylamine hydrochloride (53 mg, 0.76 mmol). The solution was stirred at room temperature for 14 h then diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated by reduced pressure yielding a yellow oil that was purified by flash chromatography (50% EtOAc in hexanes). Purification afforded 6-phenylimidazo[1,2-*a*]pyrazine 7-oxide (**18**) (37 mg, 71%) as a yellow oil. ^{1}H NMR δ 8.75 (1H, s), 8.08 (1H, s), 7.73 (1H, d, J=1.4 Hz), 7.65–7.59 (3H, m), 7.48–7.44 (3H, m); ^{13}C NMR δ 160.6, 156.8, 156.7, 149.4, 149.3, 148.4, 147.9, 147.2, 139.7, 133.1; IR (neat) 3380, 3081, 3059, 3025, 2924, 2850, 1694, 1600, 1492, 1450, 755, 698 cm^{-1}; MS 212 (M+1, 90%), 196 (M−15, 100%); HRMS calcd for $C_{12}H_{10}N_3O$ (M+H$^+$) 212.0824, found 212.0823.

Acknowledgements

We are grateful to the Robert Welch Foundation (F-1298) and TI3D for financial support of this research.

Supplementary data

^{1}H and ^{13}C NMR spectra for all new compounds and details for the crystal structure of **11**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.099. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Hulme, C.; Lee, Y.-S. *Mol. Diversity* **2008**, *12*, 1.
2. Narasimhan, B.; Sharma, D.; Kumar, P. *Med. Chem. Res.* **2010**, *20*, 1119.
3. Aoyama, T.; Naganawa, H.; Suda, H.; Uotani, K.; Aoyagi, T.; Takeuchi, T. *Antibiotics* **1992**, *45*, 1557.
4. Kishi, Y.; Goto, T.; Inoue, S.; Sugiura, S.; Kishimoto, H. *Tetrahedron Lett.* **1966**, *29*, 3445.
5. Sanger, D. J.; Depoortere, H. *CNS Drug Rev.* **1998**, *4*, 323.
6. Lantos, I.; Bender, P. E.; Razgaitis, K. A.; Sutton, B. M.; DiMartino, M. J.; Griswold, D. E.; Walz, D. T. *J. Med. Chem.* **1984**, *27*, 72.
7. (a) Baviskar, A. T.; Madaan, C.; Preet, R.; Mohapatra, P.; Jain, V.; Agarwal, A.; Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Bharatam, P. V. *J. Med. Chem.* **2011**, *54*, 5013; (b) Haberhauer, G.; Rominger, F. *Synlett* **2003**, 780.
8. Hoang, C. T.; Bouillere, F.; Johannesen, S.; Zulauf, A.; Panel, C.; Pouilhes, A.; Gori, D.; Kuoklovsky, C. *J. Org. Chem.* **2009**, *74*, 4177.
9. Dawood, K. M.; Elwan, N. M.; Abdel-Wahabb, B. F. *Arkivoc* **2011**, 111.
10. Begunov, R. S.; Ryzvanovich, G. A. *Russ. Chem. Rev.* **2013**, *82*, 77.
11. Lovely, C. J.; Chen, Y.; Ekanayake, E. V. *Heterocycles* **2007**, *74*, 873.
12. (a) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 3183; (b) Gracias, V.; Gasiecki, A. F.; Pagano, T. G.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8873; (c) Gracias, V.; Darczak, D.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9053.
13. Barthelon, A.; Legoff, X. F.; El Kaim, L.; Grimaud, L. *Synlett* **2010**, 153.
14. Laha, J. K.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 8477.
15. Mitra, S.; Darira, H.; Chattopadhyay, P. *Synthesis-Stuttgart* **2013**, *45*, 85.
16. Laroche, C.; Li, J.; Freyer, M. W.; Kerwin, S. M. *J. Org. Chem.* **2008**, *73*, 6462.
17. Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980.
18. Das, B.; Reddy, G. C.; Balasubramanyam, P.; Salvanna, N. *Synthesis* **2011**, *5*, 816.
19. Das, B.; Salvanna, N.; Reddy, G. C.; Balasubramanyam, P. *Tetrahedron Lett.* **2011**, *52*, 6497.
20. Laroche, C.; Kerwin, S. M. *J. Org. Chem.* **2009**, *74*, 9229.
21. Laroche, C.; Kerwin, S. M. *Tetrahedron Lett.* **2009**, *50*, 5194.