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Synthesis of 2-Dimethylaminoimidazole Derivatives: A New Access to Indolyl-imidazole Alkaloids of Marine Origin.

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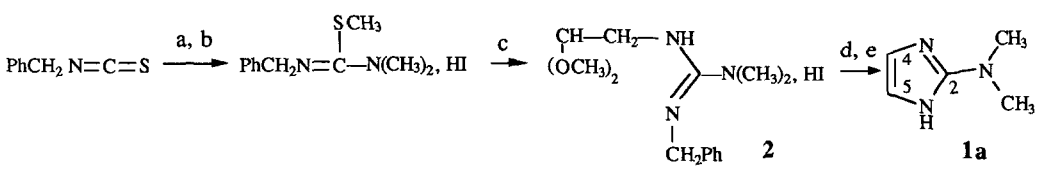
Abstract : The first preparation of 2-dimethylaminoimidazole **1a**, a structural feature of several marine products was undertaken and its reactivity investigated. The synthesis of natural alkaloids **5** and **12b** was achieved by direct coupling of the easily accessible oxidized 2-dimethylaminoimidazoles **7** and **8** with indole-3-carboxaldehyde and indole respectively, demonstrating the usefulness of this approach for other structurally related natural products.

Marine products are among the most promising sources of new and biologically active molecules. Certain metabolites possessing a cyclic guanidine subunit exhibit an interesting pharmacological activity. This cyclic guanidine moiety is most frequently found in the guise of a 2-aminoimidazole which may or may not be joined to other heterocycles.[1] In contrast to the well known 2-aminoimidazole, the 2-dimethylaminoimidazole substructure **1a** has less often been encountered in nature[2,3,4] and has not yet been synthesized. Its preparation as a starting material for many marine alkaloids was undertaken and its reactivity studied.We have therefore sought expedient, cheap and efficient syntheses of **1a**. Classical methods of imidazole synthesis could not be applied to the preparation of **1a**. For instance, the reaction of dimethylguanidine with halogenoaldehydes[5a] or the coupling of imidates with aminoacetaldehydes[5b] did not yield the expected compound. Furthermore, neither the selective methylation of 2-aminoimidazole[5c] nor the nucleophilic substitution at position 2 of 2-methylthioimidazolium[5d] provided us with the desired reaction product **1a**. At last, the reaction of benzyl dimethylthioimidate[6] and

Scheme 1

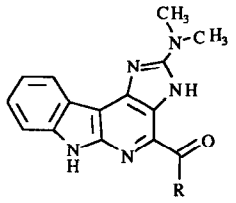


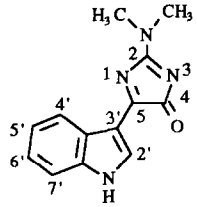
a: $HN(CH_3)_2$, toluene, 50°C, 6 h.
b: CH_3I / $CHCl_3$, reflux, 4 h.
c: $H_2NCH_2CH(OCH_3)_2$, isopropanol, reflux, 6 h.
d: HCl / isopropanol, reflux
e: HCO_2NH_4, Pd/C, MeOH, reflux, 30 mn

Overall yield 83%

aminoacetaldehyde dimethylacetal gave easily guanidine **2** whose cyclisation (scheme 1), afforded imidazole **1a**[7] with a 83% overall yield after removal of the benzyl protective group.

Among marine metabolites, the cytotoxic indole alkaloids grossularines **3** and **4**, isolated from *Dendrodoa grossularia*[2] possess a cyclic guanidine moiety in the form of a 2-dimethylaminoimidazole subunit. From the same marine organism, the immunomodulating 2-(dimethylamino)-5-(1*H*-indol-3-yl)-4*H*-imidazol-4-one **5**[3] has been isolated.

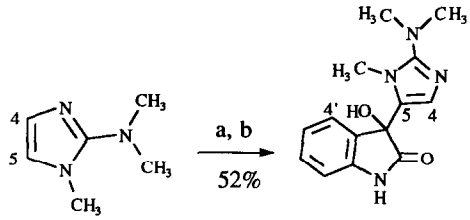




R = indolyl **3**
R = *p*-hydroxy phenyl **4**

5

With the synthesis of grossularines **3** and **4** in view, we next examined the coupling of **1a** with indole derivatives. The easily available isatin possessing electrophilicity at position 3 as well as a functionnality in position 2 appeared especially convenient. Indeed, 2-dimethylamino-1-methylimidazole **1b** after selective metallation[8] at position 5 with *sec*-BuLi / THF followed by coupling with isatin (reflux, 5h) afforded hydroxyoxindole **6**[9] in 45% yield. The next steps for the synthesis of **3** or **4** will require the protection of the indole nitrogen and the more difficult metallation in position 4 of the imidazole ring.

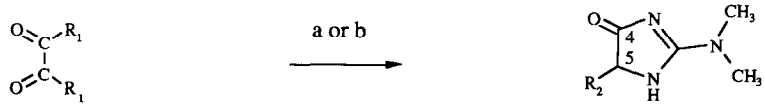


1b **6**

a : *sec*-BuLi/THF, 1 eq ; b : isatin, reflux, 5 h.

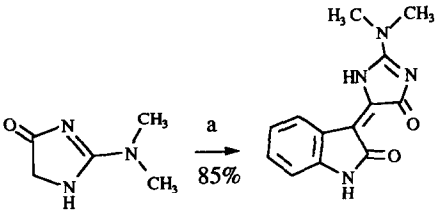
For the same purpose, oxidized derivatives of **1a** may be used without the need for protective groups. Thus 2-(dimethylamino)-1,5 dihydro-4*H*-imidazol-4-one **7** possesses a nucleophilic center in position 5 while the more highly oxidized derivative 2-(dimethylamino)-1*H*-imidazole-4,5-dione **8** is an excellent electrophile. The condensation of dimethylguanidine with glyoxal (scheme 2) constitutes an interesting one step alternative to a previously reported synthetic method[10] for **7**. Moreover the reaction of dimethylguanidine with ethyl oxalate led to the synthesis of **8**[11] which has not yet been described.

Scheme 2



R_1=H a : dimethylguanidine.HCl / H_2O, reflux, 8h. **7** R_2=H_2 52%
R_1=OCH_2CH_3 b : dimethylguanidine / MeOH, reflux, 2h. **8** R_2=O 85%

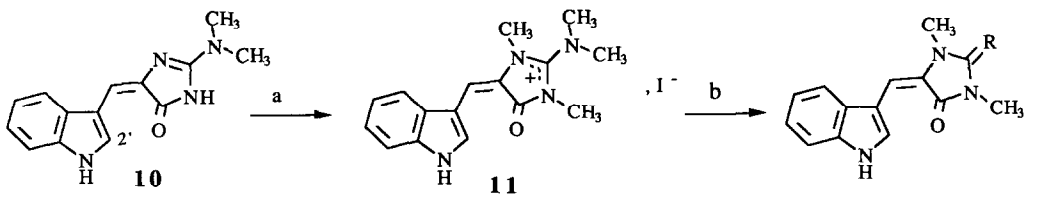
In fact, mere heating (neat, 180°C for 30 minutes) of isatin and imidazolone **7**, gave an almost quantitative yield (95%) of compound **9**[12], a suitable starting material for the synthesis of grossularines **2** and **3**, which is actually in progress.



7 9

a : isatin, 180°C, 30 mn

Furthermore, heating imidazolone **7** with indol-3-carboxaldehyde under similar conditions gave compound **10**[13] structurally related to the anticancer alkaloid aplysinopsin **12a**.[14] According to our investigation on the reactivity of imidazolium compounds[15], the closely related metabolite **12b**, isolated from the sponges *Thorecta aplysinopsis*[14a] and *Tubastraea* sp.[14f] was easily obtained by methylation of **10** and subsequent alkaline hydrolysis of the imidazolium intermediate **11**.



10 **11**

a: CH_3I, DMF, r.t., 48 h. b: KOH 1N / EtOH, reflux , 2 h. R=O **12a**

R=NH **12b**

Finally, coupling of dione **8** with indole in CF_3COOH provided us with a straightforward and efficient synthesis of the natural 2-(dimethylamino)-5-(1*H*-indol-3-yl)-4*H*-imidazol-4-one **5** in 80% yield. The easy access to this compound has allowed us to refine its structure by NMR[16] and to select the predominant tautomeric form in solution. Thus a ^1H-^{13}C correlation experiment permitted the attribution of all the carbon and hydrogen resonances corresponding to the indole aromatic ring. A specific irradiation of hydrogens H-2' (8.82 ppm) and H-4' (8.26 ppm) established the signals corresponding to quaternary carbons C-3' and C-5. In order to ascertain the predominant formula of **5** we took advantage of a simple NMR experiment: the significant increase of the spin-lattice relaxation time T_1[17] of H-2' (from 1.0s to 3.1s) following deuterium exchange with the sole mobile hydrogen indicated the vicinity of the two hydrogens which is only encountered in the indole form **5** and excluded any other tautomeric forms.

The wide range of imidazole derivatives prepared by us possessing either electrophilic or nucleophilic centres should prove useful for the synthesis of a variety natural product.

Acknowledgement: We wish to thank Dr M. Guyot for generously providing us with a reference sample of the natural compound **5**.

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7. **1a**: calc. for $C_5H_9N_3$: C% 54.03 H% 8.16 N% 37.81, found: C% 54.16 H% 8.26 N% 37.70; mp 169-171°C; IR (KBr) ν cm^{-1}: 3200 NH, 3100, 3020, 2940, 2840, 2780 CH, $N(CH_3)$, 1575, 1525, 1480, C=N, C=C; ^1H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.00 (s, 6p, $N(CH_3)_2$), 4.60 (s, 1p, NH), 6.68 (s, 2p, H-4, H-5); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ ppm: 39.5 ($N(CH_3)_2$), 117.3 (C-4; C-5), 152.3 (C-2); MS (CI, NH_3) *m/z*: 112 (MH^+).
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9. **6**: ^1H NMR (CD_3OD, 200 MHz) δ ppm: 2.70 (s, 6p, $N(CH_3)_2$), 3.85 (s, 3p, NCH_3), 6.10 (s, 1p, H-4), 6.90 (dd, 1p, Ar-H), 7.10 (td, 1p, Ar-H), 7.30 (m, 2p, Ar-H); ^{13}C NMR (CD_3OD, 50.3 MHz) δ ppm: 33.2 (NCH_3), 43.3 ($N(CH_3)_2$), 75.5 (C-OH), 111.6 (C-7'), 124.1 (Ar-C), 125.8 (C-4), 126.6 (Ar-C), 129.3 (C-5), 131.6 (C-4'), 132.2 (C-3'a), 143.2 (C-7'a), 157.6 (C-2), 179.7 (C=O); MS (CI, NH_3) *m/z*: 259 (MH^+).
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11. **8**: mp 169-171°C; IR (KBr) ν cm^{-1}: 3400 NH, 2920 $N(CH_3)_2$, 1710, 1600, C=O, C=N; ^1H NMR (CD_3OD/(CF_3COOH, 200 MHz) δ ppm: 3.22 (s, 3p, NCH_3), 3.32 (s, 3p, NCH_3); MS (CI, NH_3) *m/z*: 142 (MH^+).
12. **9**: calc. for $C_{13}H_{12}O_2N_4$: C% 60.93 H% 4.72 N% 21.87, found: C% 60.89 H% 4.92 N% 21.13; ^1H NMR (DMSO-D_6, 200 MHz) δ ppm: 3.22 (s, 3p, NCH_3), 3.23 (s, 3p, NCH_3), 6.91 (d, 7.8 Hz, 1p, Ar-H), 7.03 (t, 7.8 Hz, 1p, Ar-H), 7.24 (t, 7.8 Hz, 1p, Ar-H), 8.73 (d, 7.8 Hz, 1p, Ar-H), 10.73 (s, 1p, NH), 11.03 (s, 1p, NH); MS (EI) *m/z*: 256 (71, M^+), 70 (100).
13. **10**: calc. for $C_{14}H_{14}ON_4$: C% 66.12 H% 5.55 N% 22.04, found: C% 66.61 H% 5.61 N% 22.34; IR (KBr) ν cm^{-1}: 3168 NH, 1690, 1660, 1609, C=O, C=N, C=C; ^1H NMR (DMSO-D_6, 200 MHz) δ ppm: 3.05 (s, 6p, $N(CH_3)_2$), 6.65 (s, 1p, CH=C), 7.15-7.0 (m, 2p, Ar-H), 7.40 (d, 7.5 Hz, 1p, Ar-H), 7.86 (d, 7.5 Hz, 1p, Ar-H), 8.22 (d, 3 Hz, 1p, H-2'), 11.08 (s, 1p, NH), 11.45 (d, 3 Hz, 1p, NH); MS (EI) *m/z*: 254 (100, M^+), 156 (44), 155 (32).
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16. **5**: ^1H NMR (DMSO-D_6, 200 MHz) δ ppm: 3.35 (s, 3p, NCH_3), 3.54 (s, 3p, NCH_3), 7.3 (m, 2p, H-5', H-6'), 7.6 (m, 1p, H-7'), 8.25 (m, 1p, H-4'), 8.82 (m, 1p, H-2'), 12.5 (s, 1p, NH); ^{13}C NMR (DMSO-D_6, 50.3 MHz) δ ppm: 37.2 (NCH_3), 38.6 (NCH_3), 106.7 (C-3'), 112.9 (C-7'), 122.2 (C-4'), 122.6 (C-5'), 123.9 (C-6'), 126.1 (C-3'a), 137.1 (C-7'a), 138.2 (C-2'), 169.5 (C-2), 181.3 (C-4), 182.2 (C-5).
17. Determined in DMSO-D6 by the inversion-recovery technique.

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