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Synthesis of 2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones by the domino Michael addition retro-ene reaction of 2-alkoxyiminoimidazolidines and acetylene carboxylates

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Abstract—2-Alkoxyiminoimidazolidines **2**–**3** react with acetylene dicarboxylates and ethyl phenylpropiolate to give 8-alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones **C**, which subsequently undergo a sterically induced multihetero-retro-ene fragmentation to give imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones **4**–**7** together with formaldehyde or benzaldehyde. On the other hand, a similar reaction of **2**–**3** with ethyl propiolate gives corresponding 8-alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones **8**–**10**. The unsubstituted imidazo[1,2-*a*]pyrimidin-5(1*H*)-one **11** can be prepared by retro-ene reaction of **9** upon prolonged heating in refluxing ethanol. A direct synthetic approach to 1-formyl-7-phenyl-imidazo[1,2-*a*]pyrimidine-5(1*H*)-one **14** is reported using DMF/sulfonyl chloride as a new Vilsmeier-type *N*-formylating reagent.

1. Introduction

Imidazo[1,2-*a*]pyrimidine-5-ones possess diverse biological activities and this structural motif is present in analgesics and inflammation inhibitors[1,2] benzodiazepine receptor ligands[3] as well as insecticidal, acaricidal and nematocidal agents.[4] The structural feature of imidazo[1,2-*a*]pyrimidine nucleus is related to the purine ring system, and therefore, we were interested in the synthesis of various substituted compounds of type **A** and **B** (Fig. 1) in anticipation of their anticancer activity.

The existing methods for building up the imidazo[1,2-*a*] pyrimidine core, which include the elaboration of 2-aminopyrimidines[5] or reaction of 2-aminoimidazoline with acetylene carboxylates,[1] are either multistep procedures or require ion exchange chromatography to obtain the free base of 2-aminoimidazoline. Moreover, the above methods are not general and the parent compound **B** (R, R^1=H) was not obtained.

Herein we report a new strategy for preparation of the compounds of type **A** and **B** based on two consecutive reactions: the well-established reaction of 2-aminoimidazolines with acetylene carboxylates[1], which leads to 2,8-dihydroimidazo[1,2-*a*]pyrimidin-5(3*H*)-ones (**A**, R= alkoxyl), and the retro-ene fragmentation associated with N^1-alkoxyamidine[6,7] giving rise to the formation of 2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones (**B**).

2. Results and discussion

The domino reactions have been defined as a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and where the subsequent reaction results as a consequence of the functional group formed in the previous step.[8,9]

In developing a new strategy for the synthesis of

2,8- dihydroimidazo[1,2-*a*] pyrimidin-5(3*H*)-ones

2,3- dihydroimidazo[1,2-*a*] pyrimidin-5(1*H*)-ones

Figure 1. Structures of imidazo[1,2-*a*]pyrimidin-5-ones.

Keywords: 2,3-Dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones; 8-Alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones; Domono Michael addition retro-ene reacion; N-alkylation; N-acylation; N-formylation; X-ray crystal structure analysis.
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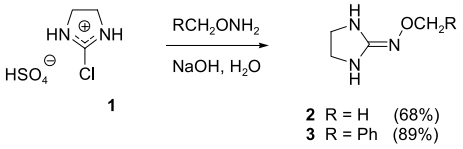
imidazo[1,2-*a*]pyrimidin-5-ones, we first focused on the ability to synthesize a bis-nucleophilic 2-alkoxyiminoimidazolidine that could undergo cyclocondensation upon treatment with acetylene carboxylates. As illustrated in Scheme 1, the desired 2-alkoxyiminoimidazolidines **2** and **3** were obtained in 68–89% yield from 2-chloro-4,5-dihydroimidazole (**1**) and commercially available *O*-methyl- and *O*-benzyl-hydroxylamines. The molecular structure of these compounds was confirmed by X-ray crystal structure analysis of **3** [CCDC 259437].



Scheme 1. Preparation of 2-alkoxyiminoimidazolidines **2** and **3**.

Novel reagents **2** and **3** thus developed were first utilized for the preparation of known[1] imidazo[1,2-*a*]pyrimidin-5-ones **4** and **7** as well as novel derivatives **5** and **6** as shown in Scheme 2. The two reagents were each reacted with acetylene dicarboxylates, ethyl phenylpropiolate or ethyl butynoate in suitable alcohol at reflux. The reaction sequence involves as the key intermediate, 8-alkoxyimidazopyrimidine **C**, which eludes isolation under the reaction conditions, and undergoes subsequent retro-ene fragmentation with simultaneous extrusion of aldehyde. Formaldehyde was trapped by dimedone, while the presence of benzaldehyde was confirmed by isolation of its 2,4-dinitrophenyl-hydrazone derivative.

It should be noted that the reaction of **2** and **3** with less reactive ethyl butynoate required 10 h to reach completion. The end products **4** and **7** were found to be identical in all respects (mp, IR, NMR and MS) with authentic samples synthesized independently.[1]

The fact that compounds **4**–**7** could be obtained without contamination by alternative products of type **D** (Scheme 2) underlines regiospecificity of the reaction. In order to identify nucleophilic sites in 2-iminoimidazolidine and 2-methoxyiminoimidazolidine (**2**) atomic charges were calculated.[15] As shown in Figure 2, introduction of an alkoxy group into 2-iminoimidazolidine evidently lowers the

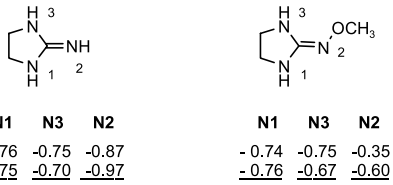


Figure 2. Calculated[15] atomic charges and charges derived from the electrostatic potential (underlined) of the nitrogen atoms of 2-iminoimidazolidine and 2-methoxyiminoimidazolidine (**2**).

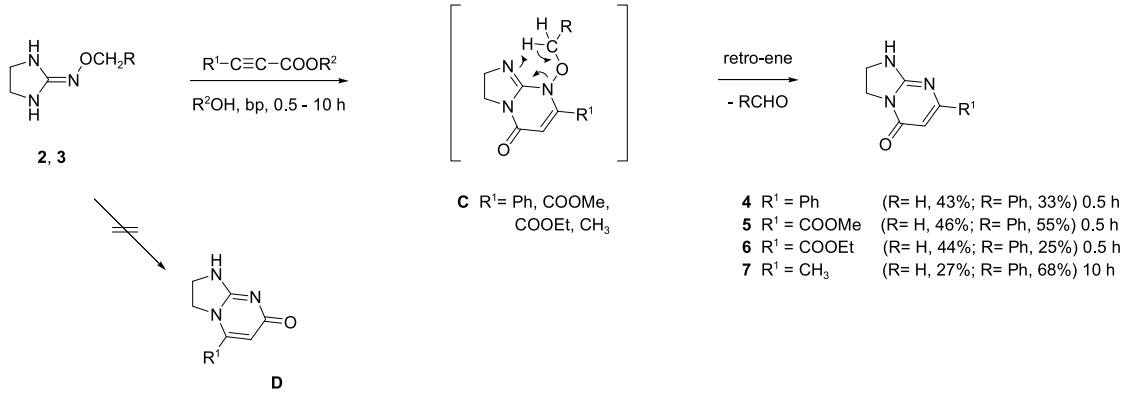
nucleophilicity of the exocyclic nitrogen atom sufficiently to prevent reaction with carboxylate.

Having established that the domino reaction takes place with both **2** and **3**, our attention was turned to its primary purpose: its ability to provide parent 2,3-dihydroimidazo[1,2-*a*]pyrimidine-5(1*H*)-one (**11**).

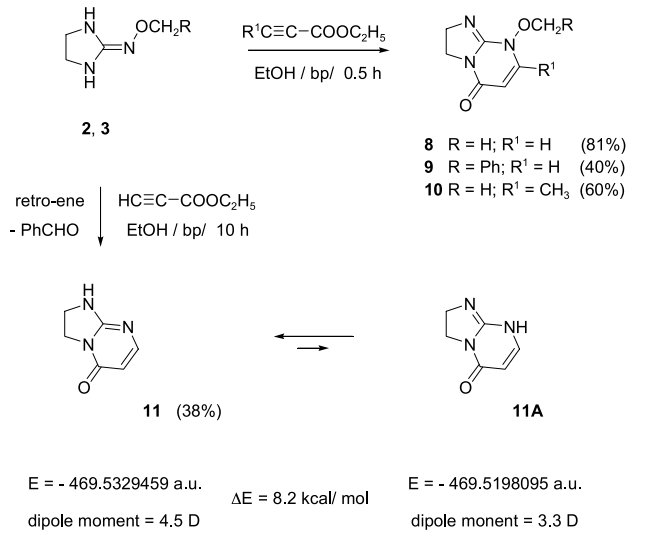
The reaction of **2** and **3** with ethyl propiolate in boiling ethanol for 0.5 h led to the formation of 8-alkoxyimidazo[1,2-*a*]pyrimidin-5-ones **8** and **9** (Scheme 3), the molecular structure of which was confirmed by X-ray crystal structure analysis [CCDC 259433 (**8**); CCDC 259436 (**9**)]. A similar reaction of 2-methoxyiminoimidazolidine (**2**) with ethyl butynoate gave 8-methoxyimidazo[1,2-*a*]pyrimidin-5-one (**10**) in 60% yield.

Apparently, the 8-alkoxy derivatives **8**, **9** and **10** are less reactive than **C** under identical conditions and can be separated from the reaction mixture in 81, 40 and 60% yield, respectively. It is well known that rates of retro-ene reactions may be enhanced[10–12] or diminished[13,14] by steric effects. The difference in reactivity between the **C** and **8**–**9** is presumably the result of the steric augmentation, i.e. the retro-ene process is induced by steric hindrance caused by bulky substituents at position 7 of **C**. The steric hindrance between the 7-phenyl or 7-alkoxycarbonyl and 8-alkoxy groups in **C** inhibits free rotation of the latter, which results in a fixed conformation that is conductive to a retro-ene mechanism.

We examined several reaction parameters including solvent, temperature, reaction time and type of bis-nucleophilic reagent **2** and **3**. At room temperature or shorter reaction time, the imidazopyrimidine **9** formation was incomplete. However, at higher temperature and reaction time greater



Scheme 2. Preparation of imidazo[1,2-*a*]pyrimidin-5-ones **4**–**7**.



Scheme 3. Reaction of 2-alkoxyiminoimidazolidines **2**–**3** with ethyl propiolate and ethyl butynoate.

than 10 h, the reaction of **3** with ethyl propiolate gave the desired parent compound **11** in 38% yield (Scheme 3). In contrast, an analogous reaction of **2** failed to give compound **11** and the 8-alkoxy derivative **8** was obtained as a sole product.

The ab initio geometry optimization at HF/6-31G** level[15] was performed on the imidazopyrimidin-5-one **11** to examine its two possible tautomers **11** and **11A** as shown in Scheme 3. These computations revealed that the N1–H tautomer **11** was favored over N8–H tautomer **11A** by 8.2 kcal/mol. On the basis of their calculated dipole moments, **11** (4.5 Debye) would be predicted to predominate over **11A** (3.3 Debye) in polar solvents. It was shown by NMR spectroscopy that the low-energy tautomer **11** is present in DMSO-d_6 solution. The methylene groups of the imidazoline moiety are nonequivalent, and the NOE was observed between an upfield-shifted C2–H protons and the N–H proton (Supplementary data).

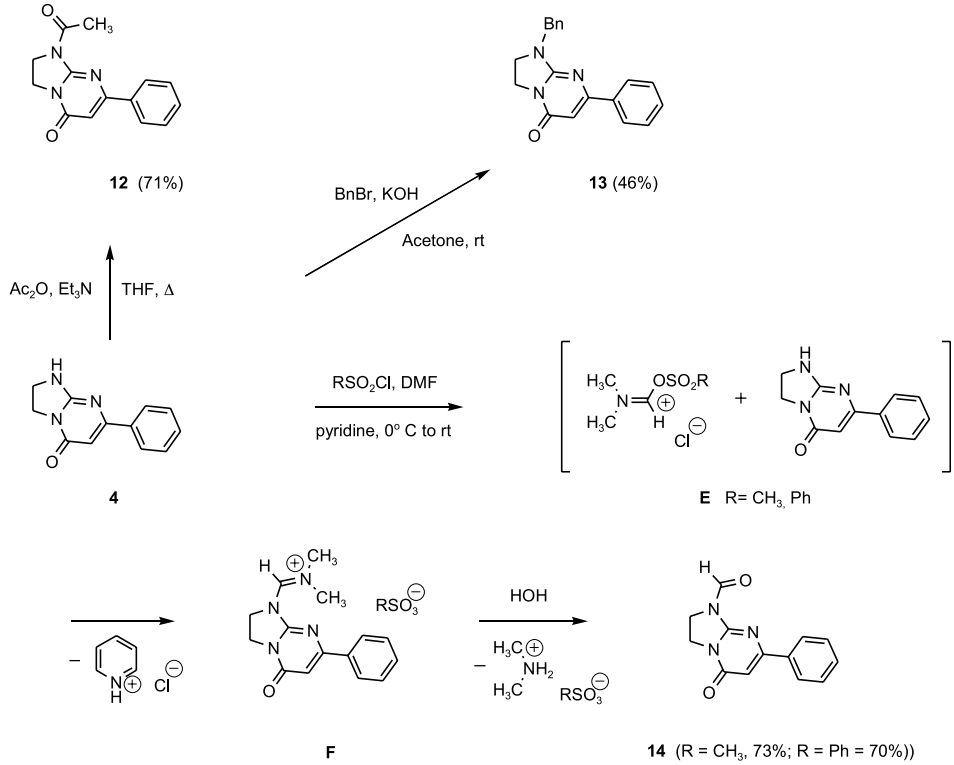
Acetylation of **4** with acetic anhydride and alkylation with benzyl bromide occurred exclusively at the site of the imidazolino nitrogen to furnish **12** and **13**, respectively, in good yields (Scheme 4).

We have also attempted to prepare 1-phenylsulfonyl- and 1-methanesulfonyl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one by treatment of **4** with corresponding sulfonyl chloride in pyridine/DMF. However, we were surprised to observe that the 1-formyl derivative **14** was obtained instead.

A possible mechanism for this reaction is outlined in Scheme 4. Initial reaction of sulfonyl chloride with dimethyl formamide gives a new type of Vilsmeier reagent **E** (*N*,*N*-dimethylphenylsulfonyloxymethylene-ammonium chloride) which then reacts under mild reaction conditions with **4** to give the amidinium salt **F**. Hydrolyis of **F** upon work-up completes the sequence.

It should noted that the use of DMF to formylate secondary amines was previously reported using chlorotrimethylsilane and imidazole[16], *tetra*-butylchloro-dimethylsilane and *N*,*N*-dimethyl-4-aminopyridine[17] as well as DMF acetals.[18]

The structures of **13** and **14** were unequivocally established



Scheme 4. Preparation of 1-acetyl-, 1-benzyl- and 1-formyl derivatives of **4**.

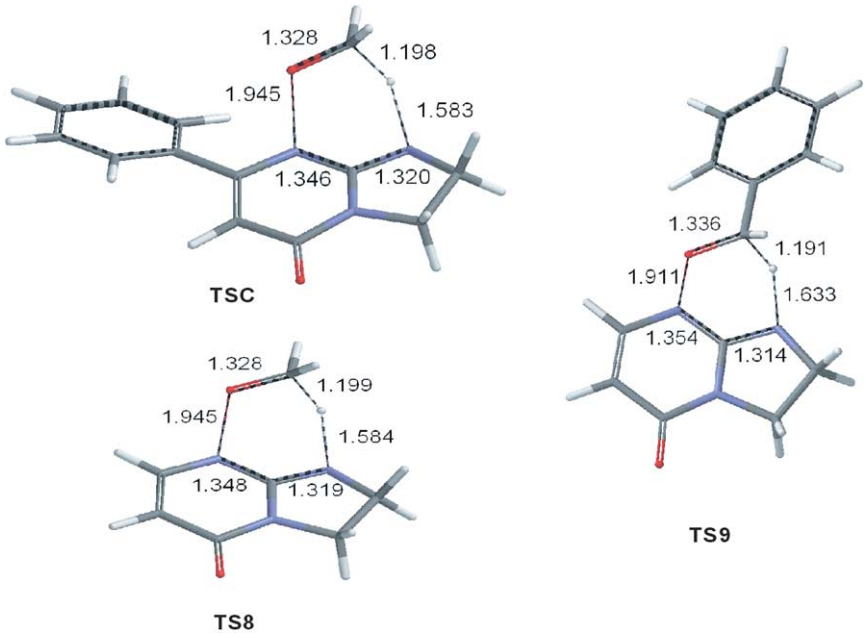


Figure 3. Calculated transition states **TSC**, **TS8** and **TS9**.

by X-ray crystal structure analysis [CCDC 259434 (**13**); CCDC 259435 (**14**)].

The one-pot procedure developed for the conversion of 2-alkoxyiminoimidazolidines (**2**–**3**) into imidazo[1,2-*a*]pyrimidin-5-ones **4**–**7** via retro-ene fragmentation of 2-O, 3-N, 5-N ene adduct merits further discussion. Previously there has been a single report of a retro ene reaction taking place in 5-(methoxyamino)-3-aryl-1,3,4-oxadiazol-2(3*H*)-ones on heating at reflux in the presence of Hünig's base.[6] To gain a closer insight into the retro-ene process, however, we still have to understand the transition state (**TS**) pertaining to the aldehyde extrusion reaction.

B3LYP/6-31G** calculations[19] were performed for 8-alkoxy-imidazopyrimidines **C** (R=H, R^1=Ph), **8** and **9**, reacting to imidazopyrimidines **4** or **11** and formaldehyde or benzaldehyde via transition states **TSC**, **TS8** and **TS9** (Fig. 3). Table 1 lists the bond lengths of interest in the reactants and transition states. In all cases the chair **TS** features the transfer of a hydrogen atom from methyl or methylene group to the nitrogen atom of the amidine moiety with lengthening of the N–O bond compared to the starting material [1.945 Å in **TSC** (1.385 Å in **C**); 1.945 Å in **TS8** (1.390 Å in **8**); 1.911 Å in **TS9** (1.388 Å in **9**)] and the long bond lengths (1.583–1.633 Å) of the N–H forming bonds, i.e. the N–O bond cleavage is more advanced than N–H bond formation. The IRC calculations confirmed that the breakage of two bonds (O–N and C–H) with loss of RCHO from **C**, **8** and **9** is asynchronous.

The calculated activation energies, presented in Table 2, give a barrier for **TSC** of 29.1 kcal/mol, **TS8** of 32.6 kcal/mol and **TS9** of 30.0 kcal/mol.

As shown in Table 2, the reaction of 8-benzyloxy **9** is calculated to be exothermic by −43 kcal/mol, 11 kcal/mol more than the 8-methoxy derivative **8**. The highly favorable thermodynamics associated with the reaction is due largely to the formation of the very strong carbon-hetero (C=O) double bond at the expense of the energy required to break the weak hetero-hetero (N–O) single bond. Apparently, the exothermicity of the fragmentation reaction of **9** is higher than in the case of **8** because of the conjugation in the benzaldehyde product.

Table 1. Bond lengths of reactants and transition states for the retro-ene reactions calculated at the B3LYP/6-31G** level

Structure	HC1	C1O2	O2N3	N3C4	C4N5	N5H
C	1.092	1.443	1.384	1.386	1.280	
TSC	1.198	1.328	1.945	1.346	1.320	1.583
8	1.092	1.442	1.390	1.388	1.279	
TS8	1.199	1.328	1.945	1.348	1.319	1.584
9	1.093	1.463	1.388	1.386	1.281	
TS9	1.191	1.336	1.911	1.354	1.314	1.633

Table 2. Relative energies (kcal/mol) for the retro-ene reactions of **C**, **8** and **9** (Schemes 2 and 3) calculated at the B3LYP/ 6-31G** level

C	TSC	11+formaldehyde	8	TS8	11+formaldehyde	9	TS9	11+benzaldehyde
0	29.1	−35.4	0	32.6	−31.7	0	30.0	−43.3

The above results indicate that the steric hindrance serves as a partial driving force for the retro-ene reaction of **C**, while the higher reactivity of **9** in comparison with **8** is due to thermodynamic factors.

Samples of the compounds **4**, **5**, **8** and **12**–**14** were submitted to the National Cancer Institute for screening against human tumor cell lines. In the primary anticancer assay, compound **13** at concentration 10^{-4} M was found to reduce the growth of cell lines to 8% (NCI–H460, non-small cell lung cancer) and 25% (MCF-7, breast cancer), respectively.

3. Conclusions

The results presented in this paper illustrate the generality of the retro-ene reaction which takes place upon heating N^1-alkoxyamidine-containing compounds in alcohol.

N,*N*-dimethylphenyl(methane)sulfonyloxymethylene-ammonium chloride generated in situ from corresponding sulfonyl chloride and DMF in pyridine solution serves as a new Vilsmeier-type *N*-formylating reagent.

4. Experimental

4.1. General

Melting points determined on a Boetius melting point apparatus and are not corrected. IR spectra were recorded on a FTIR Perkin Elmer 1600 apparatus using a mixture of the compound and KBr. ^{1}H and ^{13}C NMR spectra were taken on a Varian Unity Plus-500 spectrometer at 500 and 125 MHz, respectively. Chemical shifts were measured relative to the residual solvent signal at 2.50 or 7.26 ppm and 39.5 or 77 ppm, respectively. MS spectra were recorded on a Finnigan MAT-95 spectrometer at 70 eV. All reagents were used directly as obtained commercially. 2-Chloro-4,5-dihydroimidazolium hemisulfate[20] (**1**) was prepared according to a previous literature procedure.

4.1.1. 2-Methoxyiminoimidazolidine (2). 2-Chloro-4,5-dihydroimidazolium hemisulfate (**1**) (5 g, 24.9 mmol) and *O*-methylhydroxylamine hydrochloride (2 g, 24 mmol) were dissolved in 10% NaOH aqueous solution (25 mL). Within 15 min another 15 mL of 10% NaOH was added portionwise. After 2 h, the solution was extracted with CH_2Cl_2. Combined organic layers were dried, evaporated to dryness and the crude product **2** was purified by flash chromatography (EtOAc/MeOH 10:1); yield 1.68 g (68%); mp 111–122 °C; ^{1}H NMR ($CDCl_3$) δ 3.46 (m, 4H, CH_2), 3.66 (s, 3H, OCH_3), 3.83 (br s, 1H, NH), 4.74 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 43.0, 61.6, 160.2; IR cm^{-1} 3390, 3204, 2935, 2883, 1655; EIMS *m*/*z* (relative intensity) 115 (M^+, 100), 100 (M^+-CH_3, 52), 70 (M^+-NOCH_3, 66). Anal. Calcd for $C_4H_9N_3O$: C, 41.73; H, 7.88; N, 36.50. Found: C, 42.25; H, 7.68; N, 37.01.

4.1.2. 2-Benzyloxyiminoimidazolidine (3). 2-Chloro-4,5-dihydroimidazolium hemisulfate (**1**) (1.65 g, 8.12 mmol) was dissolved in 10% NaOH aqueous solution (25 mL). Then, *O*-benzylhydroxylamine (1 g, 8.12 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The product was extracted with CH_2Cl_2, dried, filtered and evaporated to dryness. Crude product **3** thus obtained was purified by crystallization from methanol; yield 1.38 g (89%); mp 127–130 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 4H, CH_2), 4.38 (br s, 1H, NH), 4.76 (s, 2H, CH_2), 4.84 (br s, 1H, NH), 7,25 (m, 5H, CH); ^{13}C NMR ($CDCl_3$) δ 43.2, 76.0, 128.0, 128.6, 128.7, 139.1, 161.1; IR cm^{-1} 3228, 2282, 1643, 1496, 1452. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.26; H, 7.14; N, 22.13.

4.1.3. 7-Phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (4). Compound **2** or **3** (4.35 mmol) and ethyl phenylpropiolate (0.76 g, 4,35 mmol) were refluxed in ethanol (6 mL) for 0.5 h. Solid that precipitated was filtered off, washed with ethanol and crystallized from ethanol; yield for **2** 0.40 g (43%); yield for **3** 0.31 g (33%); mp 274–275 °C (Ref. 1 mp 269–271 °C); ^{1}H NMR (DMSO-d_6) δ 3.62 (m, 2H, CH_2), 4.04 (m, 2H, CH_2), 6.15 (s, 1H, CH), 7.42 (m, 3H, CH), 7.92 (m, 2H, CH), 8.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 42.9, 98.5, 127.3, 129.1, 130.6, 137.9, 159.2, 162.0, 162.9; IR cm^{-1} 3125, 2898, 1678, 1610, 1555, 1438. Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 68.11; H, 5.35; N, 19.43.

4.1.4. 5-Oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyrimidine-7-carboxylic acid methyl ester (5). Compound **2** or **3** (4.35 mmol) and dimethyl acetylenedicarboxylate (0.62 g, 4,35 mmol) were heated at reflux in methanol (6 mL) for 0.5 h. Solid that precipitated was filtered off, washed with methanol, and recrystallized from DMF; yield for **2** 0.39 g (46%); yield for **3** 0.46 g (55%); mp 296–298 °C (DMF); ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H, CH_3) 3.62 (t, 2H, CH_2, J= 10 Hz), 4.03 (t, 2H, CH_2, J=10 Hz), 6.15 (s, 1H, CH), 8.31 (s, 1H, NH); IR cm^{-1} 3445, 3115, 1737, 1690, 1633, 1562, 1455; EIMS *m*/*z* (relative intensity) 195 (M^+, 84), 164 (M^+-OCH_3, 9), 137 ($M^+-COOCH_3$, 100). Anal. Calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.52; H, 4.35; N, 21.12.

4.1.5. 5-Oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyrimidine-7-carboxylic acid ethyl ester (6). Compound **2** or **3** (4.35 mmol) and diethyl acetylenedicarboxylate (0.74 g, 4,35 mmol) were heated at reflux in ethanol (6 mL) for 0.5 h. Precipitate was filtered off, washed and recrystallized from DMF; yield for **2** 0.40 g (44%); yield for **3** 0.23 g (25%); mp 289–290 °C (DMF); ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, CH_3, J=7 Hz), 3.62 (m, 2H, CH_2), 4.02 (m, 2H, CH_2), 4.22 (q, 2H, CH_2, J=7 Hz), 6.15 (s, 1H, CH), 8.34 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 14.0, 42.4, 61.3, 104.3, 154.6, 159.7, 161.4, 165.2; IR cm^{-1} 3445, 3115, 1737, 1690, 1633, 1562. Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.42; H, 5.35; N, 20.01.

4.1.6. 7-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (7). Compound **2** or **3** (1.57 mmol) and ethyl 2-butyonate (0.17 g, 1.73 mmol) were heated at reflux in ethanol (6 mL) for 10 h. Solid that precipitated was filtered off, washed with ethanol and recrystallized from 1-butanol; yield for **2** 0.065 g (27%); yield for **3** 0.16 g (68%); mp 232–234 °C (lit.[1] 228–230 °C); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H, CH_3), 3.65 (t, 2H, CH_2, J=8.6 Hz), 4.06 (t, 2H, CH_2, J=8.6 Hz), 5.52 (s, 1H, CH), 6.45 (br s, 1H, NH); IR cm^{-1} 3130, 3068, 2893,

1670, 1625, 1440. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.32; H, 5.84; N, 28.00.

4.1.7. 8-Metoxy-2,8-dihydro-3*H*-imidazo[1,2-*a*]pyrimidin-5-one (8). Compound **2** (0.5 g, 4.35 mmol) and ethyl propiolate (0.42 g, 4,35 mmol) were heated at reflux in ethanol (6 mL) for 0.5 h. The reaction mixture was concentrated to a volume of 2 mL under reduced pressure and diethyl ether (10 mL) was added. Pure compound **8** that precipitated was filtered off and washed with diethyl ether; yield 0.59 g (81%); mp 135–137 °C (diethyl ether); ^{1}H NMR (DMSO-d_6) δ 3.74 (m, 4H, CH_2), 3.86 (s, 3H, CH_3), 5.13 (d, 1H, CH, J=8.2 Hz), 7.71 (d, 1H, CH, J=8.2 Hz); ^{13}C NMR (DMSO-d_6) δ 44.5, 50.3, 64.0, 97.0, 142.7, 148.0, 159.8; IR cm^{-1} 1683, 1643, 1624, 1439. Anal. Calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.63; H, 5.75; N, 24.83.

4.1.8. 8-Benzyloxy-2,8-dihydro-3*H*-imidazo[1,2-*a*]pyrimidin-5-one (9). Compound **3** (0.3 g, 1.57 mmol) and ethyl propiolate (0.17 g, 1.73 mmol) were heated at reflux in ethanol (4 mL) for 0.5 h. Then, the reaction mixture was evaporated to dryness and the oily residue was extracted with diethyl ether. Combined organic layers were dried and evaporated to dryness. Product **9** was recrystallized from diethyl ether; yield 0.15 g (40%); mp 102–105 °C; ^{1}H NMR ($CDCl_3$) δ 4.03 (m, 4H, CH_2), 5.07 (d, 1H, CH, J=8.3 Hz), 5.21 (s, 2H, CH_2), 6.70 (d, 1H, CH, J=8.3 Hz), 7.44 (m, 5H, CH); ^{13}C NMR ($CDCl_3$) δ 31.9, 37.3, 65.8, 85.1, 116.2, 116.9, 117.4, 120.5, 129.5, 136.3, 147.0; IR cm^{-1} 3073, 2877, 1679, 1645, 1444. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.08; H, 5.03; N, 17.67.

4.1.9. 8-Metoxy-7-methyl-2,8-dihydro-3*H*-imidazo[1,2-*a*]pyrimidin-5-one (10). Compound **2** (0.5 g, 4.35 mmol) and ethyl 2-butyonate (0.48 g, 4.35 mmol) were refluxed in ethanol (6 mL) for 0.5 h. The reaction mixture was evaporated under reduced pressure and the residue was subjected to flash chromatography (AcOEt/ methanol 5:2); yield 0.47 g (60%); mp 115–119 °C; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H, CH_3) 3.95 (m, 4H, CH_2), 3.97 (s, 3H, OCH_3), 5.07 (s, 1H, CH); IR cm^{-1} 1683, 1644, 1607, 1451; EIMS *m/z* (relative intensity) 181 (M^+, 53), 151 (M^+-OCH_3, 100). Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.71; H, 6.43; N, 23.63.

4.1.10. 2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (11). Compound **3** (0.3 g, 1.57 mmol) and ethyl propiolate (0.17 g, 1.73 mmol) were refluxed in ethanol (4 mL) for 10 h. Then, the reaction mixture was evaporated to dryness, washed with diethyl ether and subjected to flash chromatography (AcOEt/MeOH 9:1); yield of product **11**: 0.08 g (38%); mp 157–161 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 3.58 (t, 2H, CH_2, J=8.8 Hz), 4.00 (t, 2H, CH_2, J=8.8 Hz), 5.54 (d, 1H, CH, J=6.3 Hz), 7.50 (d, 1H, CH, J=6.3 Hz), 7.94 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 39.5, 42.6, 102.8, 156.1, 159.3, 161.0; IR cm^{-1} 3262, 3115, 2979, 2867, 1674, 1614, 1433, 1285. Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.61; H, 5.43; N, 30.22.

4.1.11. 1-Acetyl-7-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (12). Compound **4** (0.2 g 0.93 mmol), acetic anhydride (2 mL) and Et_3N (2.5 mL) were refluxed in THF (15 mL) for 0.5 h. After cooling to room temperature, pure product **12** that precipitated was collected by filtration and washed; yield 0.17 g (71%); mp 256–257 °C (THF); ^{1}H NMR (DMSO-d_6) δ 2.72 (s, 3H, CH_3), 4.02 (s, 4H, CH_2), 6.69 (s, 1H, CH), 7.52 (m, 3H, CH), 8.08 (m, 2H, CH); ^{13}C NMR (DMSO-d_6) δ 25.3, 42.3, 102.5, 127.1, 129.1, 130.9, 136.3, 152.0, 160.8, 161.0, 169.3; IR cm^{-1} 3064, 1677, 1607, 1579, 1548, 1495. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.42; H, 5.25; N, 15.98.

4.1.12. 1-Benzyl-7-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (13). Powdered potassium hydroxide (0.7 g, 12.5 mmol) was added to a stirred suspension of compound **4** (0.5 g 2.35 mmol) in acetone (12 mL). After 5 min benzyl bromide (0.31 mL, 2.61 mmol) was added in one portion. Potassium bromide that precipitated was filtered off. The filtrate was evaporated under reduced pressure and the oily residue was subjected to flash chromatography (AcOEt); yield 0.13 g (46%); mp 167 °C; ^{1}H NMR (DMSO-d_6) δ 3.59 (t, 2H, CH_2, J=9.5 Hz), 4.01 (t, 2H, CH_2, J=9.5 Hz), 4.66 (s, 2H, CH_2), 6.25 (s, 1H, CH), 7.30 (m, 1H, CH), 7.38 (m, 4H, CH), 7.44 (m, 3H, CH), 8.01 (m, 2H, CH); ^{13}C NMR (DMSO-d_6) δ 39.8, 40.2, 98.4, 126.9, 127.8, 128.2, 128.8, 128.9, 130.4, 136.6, 137.2, 156.0, 161.6, 162.0; IR cm^{-1} 1668, 1575, 1553, 1409, 1485. Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.42; H, 5.16; N, 14.00.

4.1.13. 5-Oxo-7-phenyl-2,3-dihydro-5*H*-imidazo[1,2-*a*]pyrimidine-1-carboxaldehyde (14). To a cooled solution (0 °C) of compound **4** (0.23 g, 1.08 mmol) in pyridine (4 mL) and DMF (1 mL), benzenesulfonyl chloride (0.14 mL, 1.09 mmol) was added dropwise. After stirring for 24 h at room temperature, the reaction mixture was concentrated to a volume of 2 mL under reduced pressure. Then, water (5 mL) was added and the resulting precipitate was separated by suction and subjected to flash chromatography (AcOEt/$CHCl_3$ 1:3); yield 0.165 g (73%); mp 181–184 °C; ^{1}H NMR (DMSO-d_6) δ 4.04 (m, 4H, CH_2), 6.71 (s, 1H, CH), 7.52 (m, 3H, CH), 8.13 (m, 2H, CH), 9.34 (s, 1H, CH); ^{13}C NMR (DMSO-d_6) δ 41.4, 103.4, 127.1, 128.9, 130.9, 135.9, 152.4, 159.6, 160.7, 160.9; IR cm^{-1} 1668, 1669, 1613, 1579, 1543, 1593; EIMS *m/z* (relative intensity) 241 (M^+, 60), 212 (M^+-CHO, 100), 186 (10). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 65.22; H, 4.55; N, 16.97.

An analogous reaction of **4** with methanesulfonyl chloride gave the product **14** in 70% yield.

4.2. X-ray structure determination

The intensity data for the crystals have been collected using a diffractometer equipped with a CCD camera. The crystal structures have been solved with SHELXS-97[21] and refined with SHELXL-97.[22]

Crystal data for $C_{10}H_{13}N_3O$ (**3**, CCDC 259437): orthorhombic, space group *Pbca*, a=10.5139(4) Å, b=8.0906(3) Å, c=23.4330(7) Å, V=1993.30(12) Å^3, Z=8, λ=0.71073 Å, T=130 K, R_1=0.0331, wR_2=0.0830 for 1860 independent reflections with $I>2\sigma(I)$.

Crystal data for $C_7H_9N_3O_2$ (**8**, CCDC 259433): monoclinic, space group $P2_1/c$, $a=8.0951(11)$ Å, $b=11.7902(12)$ Å, $c=7.8891(11)$ Å, $(=93.212(8)°$, $V=751.78(17)$ Å^3, $Z=4$, $\lambda=0.71073$ Å, $T=110$ K, $R_1=0.0328$, $wR_2=0.0749$ for 1128 independent reflections with $I>2\sigma(I)$.

Crystal data for $C_{13}H_{13}N_3O_2$ (**9**, CCDC 259436): monoclinic, space group $P2_1/c$, $a=11.7377(7)$ Å, $b=12.1676(8)$ Å, $c=8.3598(6)$ Å, $\beta=93.871(5)°$, $V=1191.22(14)$ Å^3, $Z=4$, $\lambda=0.71073$ Å, $T=160$ K, $R_1=0.0391$, $wR_2=0.1068$ for 1839 independent reflections with $I>2\sigma(I)$.

Crystal data for $C_{19}H_{17}N_3O$ (**13**, CCDC 259434): monoclinic, space group $P2_1/c$, $a=13.7543(6)$ Å, $b=8.9734(4)$ Å, $c=14.0010(6)$ Å, $\beta=117.186(4)°$, $V=1537.14(12)$ Å^3, $Z=4$, $\lambda=0.71073$ Å, $T=130$ K, $R_1=0.0356$, $wR_2=0.0930$ for 2280 independent reflections with $I>2\sigma(I)$.

Crystal data for $C_{13}H_{11}N_3O_2$ (**14**, CCDC 259435): triclinic, space group, $a=7.4335(19)$ Å, $b=7.606(2)$ Å, $c=10.846(3)$ Å, $\alpha=78.19(2)°$, $\beta=75.79(2)°$, $\gamma=80.55(2)°$, $V=577.7(3)$ Å^3, $Z=2$, $\lambda=0.71073$ Å, $T=293$ K, $R_1=0.0371$, $wR_2=0.0846$ for 1290 independent reflections with $I>2\sigma(I)$.

Crystallographic data for the structure (excluding structure factors) in this paper have been deposited with the Cambridge Crystallographic data Centre (CCDC) as supplementary publication number CCDC. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road Cambridge, CB2 1EZ, UK (fax: +44-1223-336033) or e-mail: data_request@ccdc.cam.ac.uk).

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Supplementary data

Crystallographic data for the structures **3**, **8**, **9**, **13** and **14**; ^{1}H, ^{13}C and 1D NOESY NMR spectra of **11**; Cartesian coordinates, computed total energies and imaginary frequencies of transition states **TSC**, **TS8** and **TS9** are available free of charge.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.063

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