Preparation of imidazo[1,2-*c*]pyrimidinones from a chloropyrimidine and an electron poor ω-allylic amine

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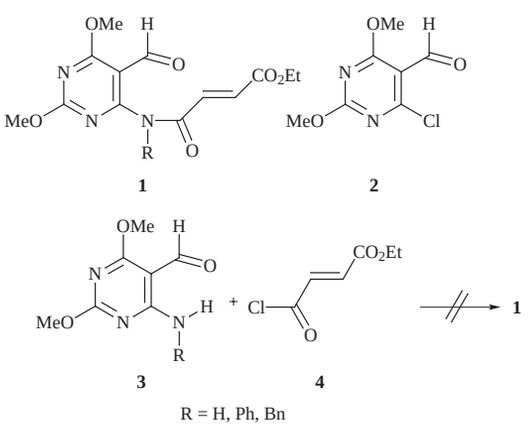
1 PERKIN COMMUNICATION

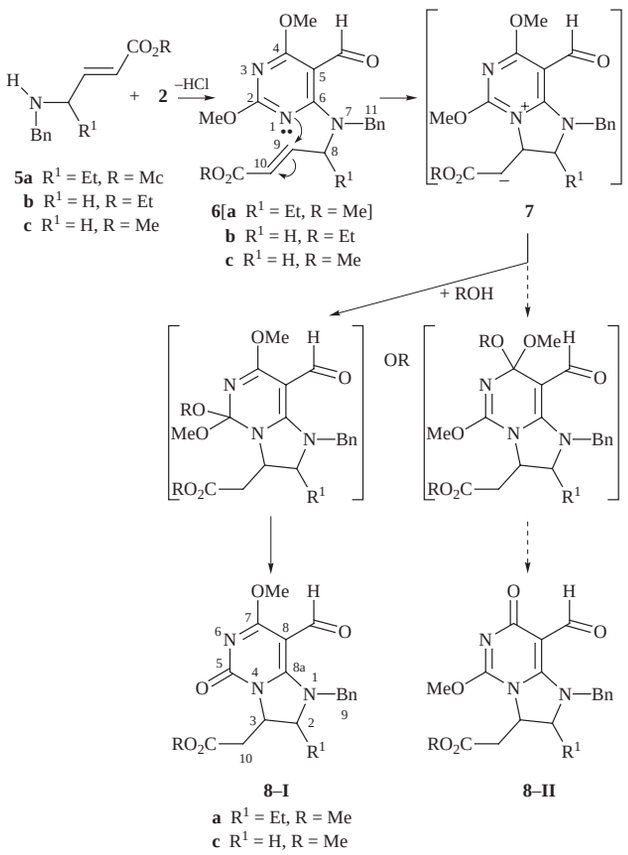
Synthesis of the title ring system by a sequential intermolecular nucleophilic displacement and intramolecular 'conjugate' addition has been achieved both as a one pot and as a stepwise procedure; an X-ray structure determination has been carried out to distinguish between the possible isomeric structures 8c-I and 8c-II.

The alkenylamidopyrimidines **1** were identified as key starting materials in an on-going project to prepare ring fused diazepines.[1] In this communication we describe some unexpected results encountered during their preparation. Attempted synthesis of **1** began with commercially available 6-chloro-2,4-dimethoxypyrimidine which was formylated according to the procedure of Plé and co-workers furnishing **2** in good yield.[2] Amination with ammonia gas or a primary amine gave the aminopyrimidines **3**, but attempts to couple **3** with the acid chloride **4** failed to deliver **1** (Scheme 1). The poor nucleophilic-



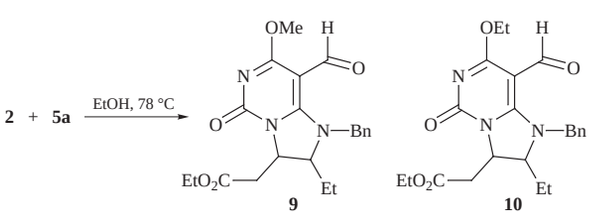
Scheme 1 *Conditions*: K_2CO_3 or $NaHCO_3$ or no base, room temp. to reflux; solvents, CH_2Cl_2, $CHCl_3$, MeCN or MeC_6H_5

ity of the amino group of **3** may be ascribed to any of a number of factors including equilibrium concentration of the tautomeric 6-imino form, intramolecular H-bonding to the adjacent aldehyde or to the electron withdrawing nature of the *o*-formyl group. Following these results we explored the introduction of an allylic amine functionality by direct reaction of **2** with allylic amines like **5**. The ω-ester substituted amine **5a**[3] was prepared. Condensation with **2** failed at room temp. and reaction occurred only after heating in refluxing MeOH (65 °C, NEt_3, 24 h) when a single new product was formed (63%). Purification by flash chromatography (SiO_2, Et_2O) and spectral analysis (^1H and ^{13}C NMR) led to a tentative identification of the product as the imidazo[1,2-*c*]pyrimidine **8a-I**, a ring system traditionally prepared either by the condensation of 4-aminopyrimidines with α-halocarbonyls or α-haloacetals, or by reaction of 4-halopyrimidines with 2-chloroethylamine.[4] On the basis of spectral data it is impossible to unambiguously distinguish between the isomeric 7-methoxy-5-oxo **8a-I** and 5-methoxy-7-oxo **8a-II** structures.



Scheme 2

Two routes to **8** have been considered; following an initial condensation the primary product **6a** undergoes an intramolecular 'conjugate' addition giving the zwitterionic species **7a**, the degradation of which may occur *via* a chloride ion induced demethylation or by the addition of one mole of alcohol (solvent) prior to deacetalation—the mole of water required for deacetalation may be available in the solvent (Scheme 2).



Scheme 3

Interestingly 'coupling' of **2** with **5a** employing EtOH as reaction solvent (78 °C) gave rise to **9** and **10**, products of alkoxy group interchange (Scheme 3).

It is known from Brown's early work that intermolecular

Table 1 Spectroscopic and microanalytical data for compounds **6c** and **8a-I** and **8c-I**

Cpd no.	Molecular formula	Found (%) [requires (%)] C	H	N	δ_H(400 MHz, $CDCl_3$, *400 MHz, C_6D_6)	δ_C(100 MHz, $CDCl_3$, *67.5 MHz, $CDCl_3$)
8a-I	$C_{20}H_{23}N_3O_5$	62.34 62.29	5.97 5.99	10.90 10.91	*10.12 (1H, s, CHO), 6.99 (5H, m, Ar-H), 5.72 (1H, d, *J* 15.3, H-9), 4.39 (1H, m, H-3), 4.17 (1H, d, *J* 15.3, H-9′), 3.62 (3H, s, OCH_3), 3.26 (1H, m, H-2), 3.06 (3H, s, OCH_3), 2.90 (1H, dd, *J* 3.0 and 16.6, H-10), 2.12 (1H, dd, *J* 9.3 and 16.6, H-10′), 1.17 and 1.02 (2 × 1H, 2 × m, CH_2CH_3), 0.49 (3H, t, *J* 7.3, CH_2CH_3)	*184.58 (CHO), 174.05 (C-7), 170.18 (CO_2Me), 155.54 (C-5, C-8a), 91.25 (C-8), 136.18, 129.09, 128.54, 128.39 (Ar-C), 66.26 (C-2), 55.49 (OCH_3), 55.34 (OCH_3), 52.64 (C-9), 51.93 (C-3), 35.30 (C-10), 25.73 (CH_2CH_3), 8.08 (CH_2CH_3)
6c	$C_{19}H_{21}N_3O_5$	61.44 61.46	5.53 5.66	11.16 11.32	10.06 (1H, s, CHO), 7.25 (5H, m, Ar-H), 6.90 (1H, m, H-9), 5.87 (1H, d, *J* 15.6, H-10), 4.76 (2H, s, CH_2Ph), 4.26 (2H, d, *J* 4.4, CH_2CH=CH), 4.05 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.72 (3H, s, CO_2CH_3)	184.91 (CHO), 175.26 (C-2), 166.31 (C-4), 165.05 (CO_2CH_3), 164.34 (C-6), 143.61 (C-9), 136.50, 128.67, 127.58, 122.71 (Ar-C), 127.71 (C-10), 97.05 (C-5), 54.95 (OCH_3), 54.75 (OCH_3), 54.70 (C-11), 51.59 (CO_2CH_3), 50.90 (C-8)
8c-I	$C_{18}H_{19}N_3O_5$	59.71 60.05	4.53 5.32	11.31 11.76	9.94 (1H, s, CHO), 7.30 (5H, m, Ar-H), 5.26 (1H, d, *J* 15.1, H-9), 5.04 (1H, d, *J* 15.1, H-9′), 4.80 (1H, m, H-3), 4.04 (3H, s, OCH_3), 3.97 (1H, t, *J* 10.8, H-2), 3.65 (3H, s, CO_2CH_3), 3.46 (1H, dd, *J* 10.7 and 4.9, H-2′), 3.29 (1H, dd, *J* 17.0 and 2.9, H-10), 2.65 (1H, dd, *J* 9.2 and 17.1, H-10′)	184.71 (CHO), 173.92 (C-7), 170.43 (CO_2CH_3), 156.64 (C-5), 153.35 (C-8a), 90.26 (C-8), 134.92, 129.00, 128.34, 128.11 (Ar-C), 55.21 (C-2), 54.84 (C-9), 53.96 (C-3), 51.99 (OCH_3), 51.40 (OCH_3), 36.19 (C-10)

amination of chloropyrimidines is sensitive to amine structure. In particular substituent(s) α to the *N*-atom are known to effect a substantial decrease in reaction rate.[5] This may well explain why thermal activation is needed to promote reaction between **2** and **5a**. Under such forcing conditions the electron rich pyrimidine *N*-atom is easily able to participate in the cyclization reaction (**6a**→**7a**). The hypothesis that **2** would condense with an α-unsubstituted amine under conditions sufficiently mild to prevent a concomitant cyclisation was tested. The amines **5b**[6] and **5c** were prepared and found to condense with **2** simply on stirring in $CHCl_3$ at room temp. in the presence of NEt_3. In each case the corresponding aminopyrimidine **6b/c** was formed in reasonable yield (63–74%) and no trace of any imidazopyrimidine could be detected.

To further probe the mechanism leading to the formation of **8** the possibility of cyclisation of **6c** by heating in boiling MeOH was investigated. It has been found that **6c** converts to **8c** (93%) after 16 h heating in refluxing bench grade MeOH. When efforts were made to dry the solvent only 50% transformation occurred after 10 h heating. No reaction products were detected when **6c** was heated in boiling, wet or dry, CH_3CN. Thus a wet nucleophilic solvent is required for imidazopyrimidinone formation and the presence of a chloride ion is not a requisite for zwitterion degradation. These observations favour the formation of **8** *via* an alcohol addition–deacetalation sequence (Scheme 2).

The product **8c** crystallised as a monoclinic crystal system and confirmation of its structure as the 7-methoxy-5-oxoimidazo[1,2-*c*]pyrimidine **8c-I** rests with a single crystal X-ray structure determination. The structure was solved by direct methods, SHELXS-97, and refined by least-squares using SHELXL-97. ORTEX was used to obtain the diagrams and the structure is depicted in Fig. 1. That **8a** has the same relative structure as **8c** is judged from the similarities between the ^{13}C resonance position of the carbonyl group in each molecule. Analysis of the magnitude of ^3J is not a reliable method for determination of the relative stereochemistry of five membered rings. In the case of **8a-I** H-2 and H-3 each resonate as multiplets (Table 1) with coupling constants which are impossible to decipher, however decoupling of the H-10 signal causes H-3 to collapse to a doublet of doublets with one large coupling constant (~9 Hz to H-10′) and one small coupling constant, ~3 Hz to H-2. In view of these observations we propose a *trans* relationship between H-2 and H-3.

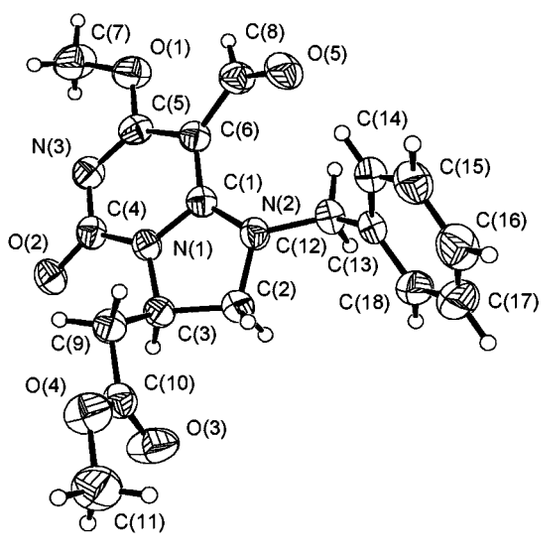


Fig. 1 Single crystal X-ray structure of **8c-I**

The resemblance of the imidazo[1,2-*c*]pyrimidine ring system to the biologically important purine bases make the molecules **8**, **9** and **10** potentially interesting pharmacophores, and the synthesis reported herein is simple and high yielding.

Crystal data for **8c-I**: $C_{18}H_{19}N_3O_5$, $M = 357.36$, monoclinic, space group $P2_1/n$, $a = 11.970(1)$, $b = 7.5911(5)$, $c = 19.279(1)$ Å, $\beta = 103.01(1)°$, $U = 1706.8(2)$ Å^3, $Z = 4$, $D_c = 1.391$ g cm^{-3}, $F(000) = 752$, Mo-Kα ($\lambda = 0.710\,69$ Å), μ(Mo-Kα) = 0.103 mm^{-1}, Nonius CAD4 diffractometer, 2080 reflections [R(int) = 0.0149] with $1873 > 2\sigma$, SHELXS-97[7] was used for direct methods structure solution and SHELXL-97[8] was used for refinement, final $R = 0.0401$ ($wR_2 = 0.1138$), Goodness of Fit = 0.929. ORTEX was used to draw the thermal ellipsoids.[9],†

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/231.

Typical experimental procedures

Methyl 2-(1-benzyl-2-ethyl-8-formyl-7-methoxy-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidin-3-yl)acetate 8a-I. To a solution of the pyrimidine **2** (0.49 mmol) and NEt_3 (0.49 mmol) in MeOH (20 cm^3) was added the amine **5a** (0.49 mmol). The mixture was heated at reflux (65 °C) for 24 h. ^{1}H NMR Spectral analysis of the crude products indicated a single new compound. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded pure **8a-I**, a yellow solid, 63%, mp 215–217 °C. Conducting the reaction in boiling EtOH (78 °C) led to **9** and **10**. Purification by flash chromatography (SiO_2, 100% Et_2O), gave **9**, a yellow solid, 24%, mp 195–197 °C (Found: C, 63.19; H, 63.0; N, 10.55. $C_{21}H_{25}N_3O_5$ requires C, 63.16; H, 6.27; N, 10.52%) and **10**, a white solid, 47%, mp 221–223 °C (Found: C, 63.96; H, 6.59; N, 10.15. $C_{22}H_{27}N_3O_5$ requires C, 63.92; H, 6.54; N, 10.17%).

Methyl 4-benzylaminobut-2-enoate 5c. A solution of benzylamine (22.3 mmol) in Et_2O (30 cm^3) at 0 °C was stirred for 15 min. A solution of methyl 4-bromocrotonate (5.59 mmol) in Et_2O (10 cm^3) was slowly added and stirring was continued for 24 h at 0 °C. The reaction mixture was washed with distilled water (3 × 50 cm^3), and removal of the solvent under reduced pressure gave crude product which was purified by flash chromatography (Et_2O: light petroleum, bp 40–60 °C, 1 : 1) to afford pure **5c**, a brown oil (65%) which was used without delay. δ_H(400 MHz: $CDCl_3$) 7.30 (5H, m, Ar-H), 7.03 (1H, m, CH_2CH=CH), 6.03 (1H, d, *J* 4.39, CH_2CH=C*H*), 3.81 (2H, s, PhCH_2), 3.74 (3H, s, OCH_3), 3.44 (2H, d, *J* 5.37, CH_2CH=CH); δ_C(400 MHz; $CDCl_3$) 166.58 (CO_2CH_3), 146.83 (CH_2CH=CH), 139.56 (C′), 128.17, 128.07, 126.86 (ArC), 120.83 (CH_2CH=*C*H), 52.94 (PhCH_2), 51.23 (OCH_3), 49.19 (CH_2CH=CH).

Methyl (*E*)-4-[benzyl(5-formyl-2,6-dimethoxypyrimidin-4-yl)-amino]but-2-enoate 6c. A solution of the pyrimidine **2** (1.98 mmol) in chloroform (25 cm^3) was stirred at 0 °C for 15 min. NEt_3 (1.98 mmol) and a solution of the amine **5c** (1.98 mmol) in chloroform (5 cm^3) were slowly added and stirring was continued for 8 h at rt. The reaction mixture was washed with brine, dried and the solvent removed under reduced pressure to afford crude product, **6c** a yellow solid which crystallized to pale yellow crystals (74%), mp 79–80 °C [Et_2O: light petroleum (9 : 11)].

Methyl 2-(1-benzyl-8-formyl-7-methoxy-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidin-3-yl)acetate 8c-I. A solution of the alkenylaminopyrimidine **6c** (0.16 mmol) in MeOH (10 cm^3) was heated at reflux (65 °C) for 6 h. Removal of solvent and purification, flash chromatography, (Et_2O: light petroleum 7 : 3) furnished **8c-I**, a white solid 93%, mp 151–153 °C (Et_2O, MeOH).

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References

1 S. Bourke and F. Heaney, *Tetrahedron Lett.*, 1995, **36**, 7527; F. Heaney and S. Bourke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 955; F. Heaney, S. Bourke, D. Cunningham and P. McArdle, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 547.
2 N. Plé, T. E. Fiquet, G. Queguiner, *J. Heterocycl. Chem.*, 1991, **28**, 283.
3 T. Tanikaga, J. Takeuchi, M. Takyu and A. Kaji, *J. Chem. Soc.*, *Chem. Commun.*, 1987, 386; R. Tanikaga, Y. Nozaki, T. Tamuara and A. Kaji, *Synthesis*, 1983, 134.
4 J. A. Montgomery and J. A. Secrist III, in *Comprehensive Heterocyclic Chemistry*, ch. 4.10, vol. ed. K. T. Potts, Pergamon, Oxford, 1984; D. R. Sliskovic, in *Comprehensive Heterocyclic Chemistry II*, ch. 8.12, vol. ed., G. Jones, Pergamon, Oxford, 1996.
5 D. J. Brown and J. M. Lyall, *Aust. J. Chem.*, 1965, **18**, 741.
6 J. W. E. Glattefeld and E. Rietz, *J. Am. Chem. Soc.*, 1940, **42**, 974; J. P. Freeman, *Org. Synth.*, 1993, **Coll. Vol. VIII**, 9.
7 G. M. Sheldrick, *Acta Crystallogr.*, *Sect. A*, 1990, **46**, 467.
8 G. M. Sheldrick, SHELXL-97 a computer program for crystal structure determination, University of Göttingen, 1997.
9 P. McArdle, *J. Appl. Crystallogr.*, 1995, **28**, 65.

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