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A one-pot domino reaction in constructing isoorotate bases and their nucleosides

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Abstract—A novel strategy, involving the coupling of enaminoesters with chlorosulfonyl isocyanate and accelerated by microwave irradiation, enables the straightforward preparation of the biologically important isoorotate bases. Extensions to nucleoside derivatives are also described.

The biosynthesis of purine and pyrimidine nucleotides is at the heart of chemical biology. In particular, the metabolic pathway for the de novo synthesis of pyrimidine bases is a relatively simple multienzymatic process that ultimately leads to orotate (uracil-6-carboxylate) as a heterocyclic precursor.[1] A large production of orotic acid results in orotic aciduria, the only genetic deficiency in pyrimidine nucleotide biosynthesis.[2] While orotate decarboxylase is prevalent in mammals and numerous bacteria, lower eukaryotes possess isoorotate decarboxylase and, hence isoorotic acid (uracil-5-carboxylic acid) is the precursor of pyrimidine bases in such organisms.[3] Metal derivatives of both orotate and isoorotate offer promising pharmacological perspectives.[4,5] In addition, uracil nucleosides modified at C-5 exhibit HIV-targeting antiviral activity,[6] and their hydrogen-bonding ability make them excellent candidates in constructing non-covalent supramolecular networks.[7–9]

The preparation of pyrimidine bases, especially uracils, represents a current synthetic goal.[10,11] Herein, we describe a novel and efficient route to uracils, exemplified by the isoorotate nucleus, by reaction of enaminoesters with isocyanates. Although transformations involving enamines and iso(thio)cyanates are well documented,[12] reaction outcomes depend on the structure of the starting materials leading to several addition or substitution products. Amino hydrouracils were obtained as high-temperature by-products from disubstituted tertiary enamines and isocyanates,[13] whereas milder conditions provided β-amino-β-lactams.[14] Primary enamines react with isocyanates to afford uracil derivatives, although this transformation arises from the well-known N-acylation of enamines (i.e., nucleophilic attack of the amino group to the electrophilic carbon of the heterocumulene), followed by further cyclization of the resultant intermediates to uracils.[15] Recently, this strategy has been applied to the synthesis of fluorinated (thio)uracils in solution and on solid phase.[16]

In our preliminary screening we tested the unprecedented condensation of N-substituted aminomethylene malonates (**1** and **2**) with excess of phenyl isocyanate (1:3 molar ratio). Such reactions were certainly disappointing as moderate yields of **3** (68%) or **4** (57%) could only be obtained after 20 days in refluxing toluene (Scheme 1). Starting from **2**, the enaminoamide **5** (38%) was also isolated as by-product.

The above transformations could be improved by non-conventional techniques such as ultrasonic irradiation (cleaning bath at 35 kHz; yet these reactions were incomplete after one week) and especially microwave irradiation (Milestone reactor, approx. 1 h). Remarkably, such an acceleration also avoided the formation of side products like **5**.

Keywords: Enamines; Isocyanates; Isoorotates; Microwaves; Nucleosides.
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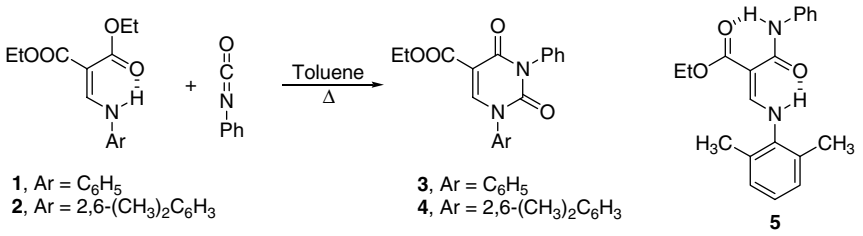
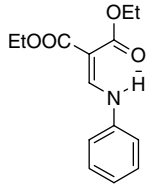
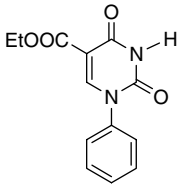
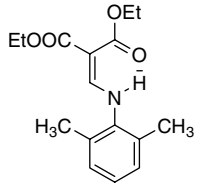
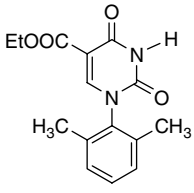
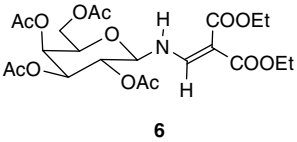
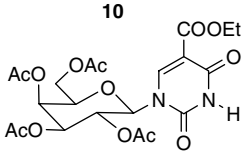
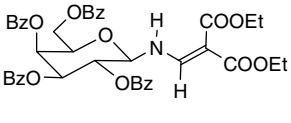
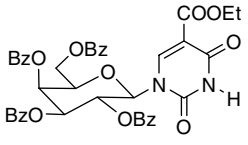
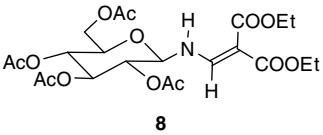
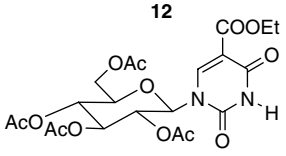


Scheme 1.

In the search for milder conditions, attention was paid to the more reactive electrophile chlorosulfonyl isocyanate. With this reagent, coupling of **1** took place in toluene at reflux within 48 h. To our delight, the labile chlorosulfonyl group was removed during the work-up protocol (involving SiO_2-based chromatography),[17] which provides straightforward access to the isoorotate nucleus (Table 1). Irradiation with microwaves largely accelerated this transformation (reactants essentially disappeared after 1 h). It now could be achieved at a lower temperature (in refluxing benzene), although the uracil derivative **9** was isolated in lower yield (44% vs 60% under conventional heating), presumably due to decomposition. The irradiated reaction of **2** with chlorosulfonyl isocyanate occurred within 30 min and the isoorotate **10** could be isolated in 77% yield.[18] Crystals of this derivative, well-suited for X-ray diffraction analysis, could be obtained.[19] It is worth noting that the solid-

Table 1. Reactions of enamines with chlorosulfonyl isocyanate

Enamine	Method[a]	Time (h)	Yield[b] (%)	Product
 **1**	A	48	60	 **9**
	B	1	44	
 **2**	B	0.5	77	 **10**
 **6**	A	72	70	 **13**
	B	1	58	
 **7**	A	48	60	 **12**
	B	1	46	
 **8**	A	48	44	 **13**
	B	1	30	

[a] Method A: toluene at reflux; Method B: MW, benzene, 80 °C.
[b] Yields refer to isolated, crystalline materials.

state structure reveals the orthogonal arrangement between phenyl and uracil moieties. As expected for a naked pyrimidine base, the crystal structure also shows the antiparallel self-assembly of the isoorotate bases associated by two N–H···O=C hydrogen bonds with a length of 2.01 Å and an angle NHO of 173.1° (Fig. 1).

We reasoned that formation of isoorotates by means of this protocol would largely be enhanced if one were also able to obtain the corresponding nucleoside derivatives. Although sugar fragments are sensitive to harsh reaction conditions, we tackled this goal in view of the facile preparation of O-protected carbohydrate-based enamines from readily available raw materials.[20] Enamines **6**–**8** reacted with chlorosulfonyl isocyanate in refluxing toluene to produce isoorotate nucleosides **10**–**12** in moderate to good yields within 2–3 days. Substantial improvement could be achieved under microwave (1-h irradiation at 80 °C), though lower yields were invariably obtained, again attributed to partial decomposition.

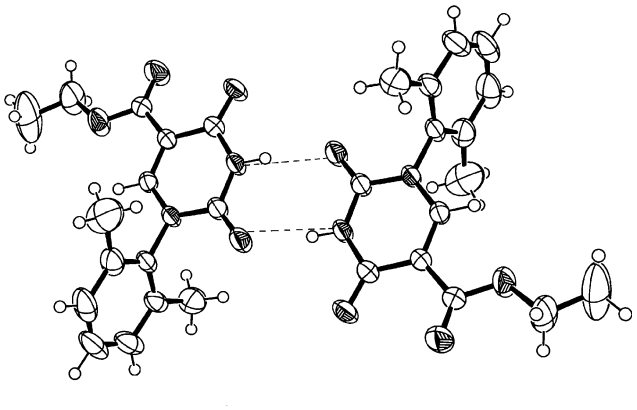
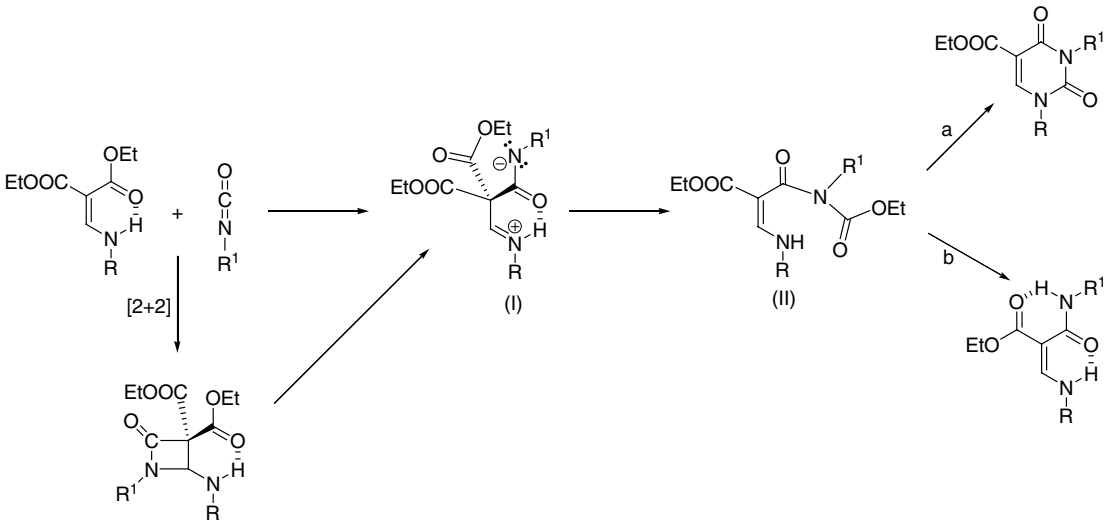


Figure 1. Solid-state diagram of **10** forming pairs owing to intermolecular hydrogen bonds.

A plausible rationale for the whole transformation is depicted in Scheme 2. This mechanistic approach is based on the well-established reactivity pattern between alkenes and isocyanates. Thus, the zwitterionic intermediate **I** could be generated either by an initial [2+2] cycloaddition followed by subsequent opening of the resulting β-lactam,[21] or by direct nucleophilic attack. That polar intermediate would further evolve into **II**, which could lead to formation of isoorotates by intramolecular reaction or the acyclic adduct by loss of the carboxyethyl group. It is often said that mechanisms can only be disapproved[22] and further studies will be undertaken to test this rationale.

The last concern to be addressed is the sensitivity of this transformation to microwave irradiation. Whilst in polar media the expected dielectric heating should be operating, no thermal effect is to be expected in apolar hydrocarbon solvents, like the present situation. The observed acceleration thus points to non-thermal effects, yet controversial, which have been rationalized by Loupy and associates based on mechanistic considerations.[23] Thus, a bimolecular reaction between neutral reactants should be assisted by microwave irradiation as the reaction goes through a dipolar transition state. If stabilization of the transition state is more pronounced than that of the ground state, this should result in enhancement of reactivity as consequence of a decrease in the activation energy, because of electrostatic (dipole–dipole type) interactions of polar molecules (or intermediates) with the electric field.

In conclusion, this communication discloses a one-pot sequential transformation that converts enamines into isoorotate derivatives by reaction with chlorosulfonyl isocyanate. The protocol can also be extended to nucleosides. We believe this novel strategy should stimulate further pursuits, and such heterocyclic products can find a niche as antimetabolites and molecular scaffolds for oligomer construction. These applications are currently under way.



Scheme 2.

Acknowledgements

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18. Preparation of compound **10**. To a solution of **2** (0.70 g, 2.40 mmol) in benzene (3.5 mL) was added dropwise chlorosulfonyl isocyanate (0.37 g, 0.23 mL, 2.5 mmol) and the mixture was then irradiated at 80 °C for 30 min. The reaction mixture was evaporated and purified by column chromatography (SiO_2, dichloromethane/diethyl ether, 21:1). The resulting product was crystallized from methanol (0.57 g, 77%). Mp 225 °C; IR (KBr) ν 3072 (N–H), 1695 (C=O, C=C), 1290 (C–O–C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H, NH), 8.22 (s, 1H, =CαH), 7.31 (t, 1H, $J = 7.6$ Hz, arom), 7.23 (d, 2H, $J = 7.5$ Hz, arom), 4.16 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3), 2.10 (s, 6H, 2× o-CH_3), 1.22 (t, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.58 (C=O), 159.46 (C=O), 152.27 (=Cα), 148.91 (CO_2Et), 135.95 (C-1, arom), 135.65 (C-2,6, arom), 130.28, 129.25 (arom), 106.16 (=Cβ), 61.70 (OCH_2CH_3), 17.93 (2× o-CH_3), 14.41 (OCH_2CH_3).
19. The atomic coordinates for compound **10** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK Crystal data for **10** (CCDC-199104), $C_{15}H_{16}N_2O_4$, $M_r = 288.30$, monoclinic, $P2_1/c$, $a = 11.4449(3)$, $b = 12.7636(3)$, $c = 11.1048(2)$ Å, $\beta = 114.5070(10)°$, $V = 1476.03(6)$ Å^3, $Z = 4$, $D_{calcd} = 1.297$ g cm^{-3}, λ(Mo Kα) = 0.71073 Å, $\mu = 0.095$ mm^{-1}, $F(000) = 608$, $T = 273(2)$ K, Goo$F^2 = 1.036$, independent reflections = 2602 [$R_{int} = 0.0673$] of a total of 14,463 collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2) = 0.0537$, $wR(F^2) = 0.1359$, R(all data) = 0.0704, $wR(F^2) = 0.1474$.
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