The Synthesis of a Fungal Isonitrile Antibiotic *via* a Novel Radical Addition–Elimination Reaction

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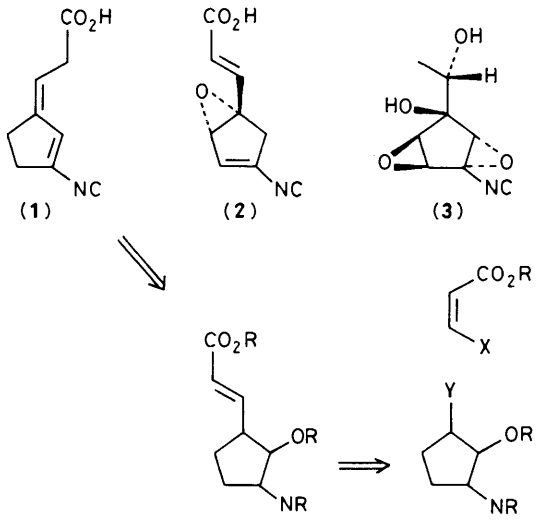
The reaction of β-stannyl acrylates with carbon radicals, generated from the corresponding bromides, to afford β-alkyl acrylates is the key carbon–carbon coupling step in a synthesis of the fungal dienyl isonitrile antibiotic (**1**).

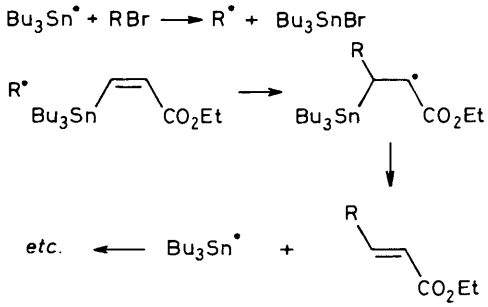
Cyclopentanoid isonitriles (**1**), (**2**), and (**3**) are a group of antibiotic metabolites of fungi in the genus *Trichoderma*. The biosynthesis of compound (**1**), referred to in our laboratory as '270' because of its u.v. absorption spectrum, has been shown to derive from tyrosine[1] but its chemistry is virtually unexplored.[2] We now report the first synthetic route to this dienyl isonitrile.

Our strategy consisted of the convergent connection of the side chain C_3 fragment to a suitably functionalised cyclopentanoid moiety, followed by elaboration of the highly unstable dienyl isonitrile functionality (Scheme 1). In view of the lack of mild and non-basic methods for the direct coupling of acrylates to highly functionalised entities, as required in Scheme 1, we have developed a new method of carbon–carbon bond formation based on a radical addition–elimination process (Scheme 2). In this method the product, *i.e.* β-substituted acrylate, is generated *directly* as a diamagnetic entity *via* the elimination of the trialkylstannyl radical. This is in contrast to the simple addition of alkyl radicals to acrylates, generating the α-propionyl radical which must be trapped for product formation. This latter process, at least in the intermolecular sense, gives rise to telomer byproducts.[3]



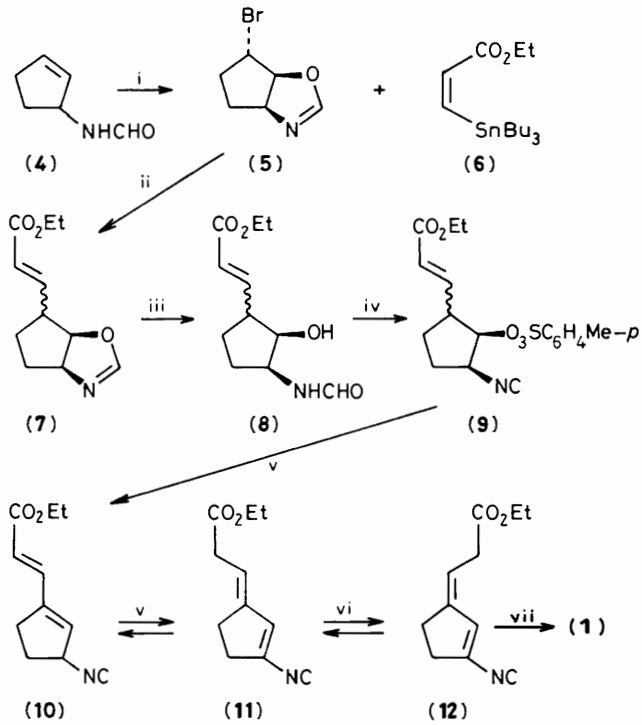
Scheme 1

Thus the formamide (**4**)[4] on treatment with *N*-bromosuccinimide (NBS) afforded the dihydro-oxazole (**5**), 60%, b.p. 42 °C/0.2 mmHg, ^{1}H n.m.r. ($CDCl_3$) 6.7 (1H, s), 5.0 (1H, d, *J* 7 Hz), 4.6 (1H, t, *J* 7 Hz), 4.3 (1H, m). The crucial carbon–carbon coupling was carried out on this substrate, at the halogenated carbon atom by reaction of (**5**) (4.3 mM) with the β-stannyl acrylate (**6**)[5] (8.8 mM) in toluene (2 ml) in the presence of hexabutylditin (0.14 mM) at 86 °C to give the dihydro-oxazoles (**7**).† These were hydrolysed *in situ* with aqueous acetic acid to the formamides (**8**) [79%, of which 70% was the *trans*, (*E*) isomer]. Concomitant dehydration of the formamides and tosylation gave the isonitriles (**9**) [32%, 50:50 mixture of *cis* and *trans*, (*E*) isomers] plus the dienyl isonitrile (**10**), 10%, u.v. (CH_2Cl_2) λ_{max} 256 nm, (ε 20,500);



Scheme 2

† The scope of this reaction is under investigation at present. Under similar conditions α-bromoacetaldehyde diethyl acetal afforded a 52% yield of ethyl 5,5-diethoxypent-2-enoate.



Scheme 3. i, NBS (1 equiv.), CH_2Cl_2, 0 °C, dark, distillation; ii, see text; iii, tetrahydrofuran (THF) (15 ml), water (2 ml), glacial acetic acid (80 μl), 25 °C, flash silica gel column chromatography; iv, *p*-$MeC_6H_4SO_2Cl$ (2.2 equiv.), Me_3N (5—10 equiv.), CH_2Cl_2, 0 °C, flash silica gel chromatography; v, DBU (1.5—10 equiv.) in CH_2Cl_2; vi, [$^2H_6$]benzene, I_2 (0.3 mol %), 25 °C; vii, LiOH (1 M), THF, room temp., 0.1 M HCl to pH 3—4, flash silica gel column chromatography.

i.r. (cm^{-1}) 2140, 1710; ^1H n.m.r. ($CDCl_3$) 7.46 (1H, d, *J* 16 Hz), 6.05 (1H, s), 5.94 (1H, d, *J* 16 Hz), 4.69 (1H, br. s). Treatment of either (**9**) or (**10**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride at room temperature effected migration of the double bond as required but yielded the *E* stereochemistry of the exocyclic double bond, since the product was an 80 : 20 mixture of diene (**11**), u.v. ($CHCl_3$) λ_{max} 273 nm (ε 21,400); i.r. (cm^{-1}) (CCl_4) 2110, 1740; ^1H n.m.r. ([$^2H_6$]benzene) 5.56 (1H, s), 5.38 (1H, m), 2.68 (2H, d, *J* 7.5 Hz) and the isomer (**10**). The same mixture was obtained on exposure of (**11**) to this base.

When the methyl ester of the natural product (**1**)‡ or the dienyl isonitrile (**11**) were converted into their kinetic enolates (lithioisopropylcyclohexylamine, −78 °C[6]) these were configurationally stable at room temperature, since quenching (D_2O) gave the original double bond isomer, with no interconversion. Consequently an alternative isomerisation was required and indeed treatment of (**11**) with iodine in benzene gave an 80 : 20 mixture of (**11**) and (**12**), from which (**12**) could be isolated by chromatography (silica gel, light petroleum–diethyl ether). Recycling the unwanted isomer (**11**) allowed a reasonable yield of (**12**) to be obtained (*ca.* 50%). Finally alkaline hydrolysis of the ester (**12**) and acidification yielded the isonitrile carboxylic acid (**1**).

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