Stereoselective Cyanosilylation Reactions in Hindered Cyclic Ketones

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Abstract: An efficient, mild and inexpensive protocol for the stereoselective construction of cyanohydrins in hindered, and in some cases, multifunctional cyclic ketones has been established.

Key words: cyanohydrin, diastereoselectivity, ketones

We have recently reported some our work for the preparation of the left[1–3] and middle fragments[4] of the synthesis of the novel antibiotic, antiviral and cytotoxic compound, oxazolomycin (**1**), and in order to address the remaining right hand side, required methodology which would permit the homologation of tetramic acid **2** at C-6, to generate an α-hydroxyaldehyde function or its synthetic equivalent. Enantiopure tetramic acid **2** is readily available using our previously published methodology by chemoselective Dieckmann cyclisation of an appropriately modified serine derivative,[5] and we had earlier shown that ketone extension using Wittig reagents is possible under forcing conditions, leading to benzoindolone products.[6] The density of functionality, along with the hindered bicyclic structure and acidity at C-7 of tetramic acid **2** clearly make homologation at C-6 a demanding step, but we report here that this can be achieved under mild conditions using the inexpensive TMSCN–ZnI_2 reagent combination at room temperature and in the absence of solvent.

Since its original report,[7] cyanosilylation has been widely used for reactions to aldehydes and simple ketones, and although effective conversions require appropriate Lewis acid catalysis,[8,9] highly efficient enantioselective reactions have been shown to be possible.[10] Developments in this area continue apace.[11–14] However, a recent report noted that, although TMSCN has been rarely used for less reactive ketones, and in particular those deactivated with α-heteroatoms, indium tribromide catalyst can be used in these cases to great effect; however, even under these conditions, sterically hindered systems exhibited lower yields.[15,16] In order to develop cyanosilylation methodology for our purposes, we needed to investigate its application to hindered cyclic ketones which also possessed acidic protons; this is an area which has been largely ignored, except for one recent report,[17] as well as a procedure reported more than 20 years ago in which a cyanohydrin was used for in situ protection of β-dicarbonyls in a reduction reaction; the cyanohydrins were not isolated in this case.[18] In a model study, we found that cyanosilylation of β-ketoesters **3a** and **3b** using TMSCN and ZnI_2 at room temperature and in the absence of solvent[19] gave excellent yields of two inseparable diastereomeric products **4a** (83%, 4:1 ratio) and **4b** (83%, 4:1 ratio), respectively after 24 hours stirring (Scheme 1). These adducts were stable to chromatography and the presence of the nitrile function was indicated by IR analysis (2230 cm^{-1});[20] no evidence for elimination to the corresponding TMS ether was apparent. Significantly, application of these mild conditions to more heavily substituted cyclopentanones **5a** and **5b** gave high yields of the products **6a**, **7a** (97%, 3:1 ratio of separable diastereomers)[21] and **6b**, **7b** (60%, mostly one diastereomer **6b** but of unassigned stereochemistry at C-3, Scheme 2).[22] Of value was our additional finding that the sense of the diastereoselectivity of these processes could be established by careful NOE analysis, provided long mixing times were used, as indicated by the presence/absence of enhancements from adjacent protons to the TMS residue (Figure 1). Thus, the major diastereomer to be formed was the one in which cyanide preferentially approached from the less hindered *exo*-face of the cyclic system, i.e. *syn*- to the ester function. Of interest was the fact that reaction of cyclohexenone **8** under these conditions gave the product **9** of 1,2-addition exclusively in 42% yield (Scheme 3), consistent with earlier findings.[7]

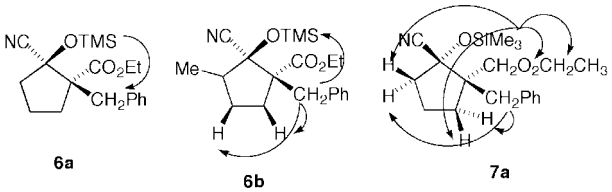

Figure 1

Encouraged by these results, we examined the reaction of tetramic acid **2**, but found that the reaction required elevated temperature, and after 24 hours at 60–90 °C, high yields (>90%) of the product **10** in a diastereomeric ratio of 2:1 could be obtained, but unfortunately in this case, NOE analysis was unproductive, and direct stereochemical assignment was therefore not possible (Scheme 4). This compound was stable, with its keto tautomeric structure evident from the presence of C(7)H/C(7)Me coupling in both stereoisomers (δ = 2.7 and 1.3 ppm, J = 7.7 Hz in one diastereomer and δ = 3.0 and 1.4 ppm, J = 7.5 Hz in the other). However, the stereochemistry at C-6 was

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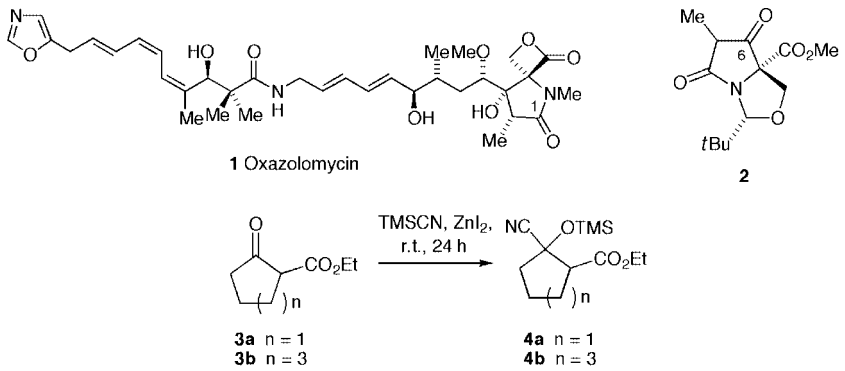
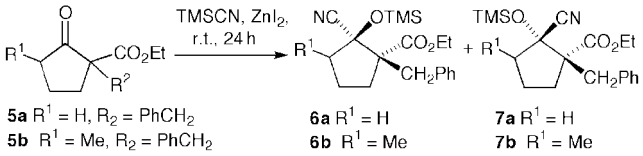
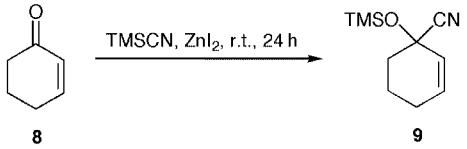


Scheme 1



Scheme 2

assigned on the basis of the results indicated above, and from NOE analysis on derivative **13** (see below); that the C-7 position is epimeric was established as indicated below. Thus, cyanide is most likely to have added to the *exo*-face of the bicyclic system in a thermodynamically controlled process. An attempt to achieve more robust protection of the TMS ether of **10** as the corresponding O-acetyl derivative gave the mixture of products **11** and **12** in 60% and 20% yields, respectively. Similarly, attempted OMEM protection by direct treatment with MEMCl and *i*-Pr_2NEt in CH_2Cl_2 gave ketene aminal **13** as a single diastereomer in 33% yield, or initial deprotection (KF, THF) followed by reaction with MEMCl and *i*-Pr_2NEt gave a 30% yield of a mixture of **14** and **15**. The fact that **13** was obtained as single diastereomer, assigned by NOE analysis as indicated in Scheme 4, indicates that the diastereomeric mixture of lactam **10** is therefore epimeric at C-7.[23]



Scheme 3

The efficacy of this procedure is evident when compared to alternative nucleophiles. For example, lithiated benzothiazole has found application for one-carbon extensions of a range of electrophilic functional groups, giving valuable synthetic intermediates.[24] However, we found that this reagent with tetramic acid **2** gave low yielding (ca. 11%) and non-specific reactions at each possible carbonyl site, to give products **16**, **17** and **18** (Scheme 4), consistent with its high nucleophilicity. NOE analysis indicated C-6 *endo*-attack of the nucleophile, presumably as a result of a kinetically preferred process; similar selectivity in the case of reductions in this system has been observed.[25]

In summary, we report here an efficient methodology for the construction of cyanohydrins from hindered and heavily functionalised ketones under mild and inexpensive conditions. Furthermore, diastereomeric assignment has been shown to be possible, using NOE and NOESY techniques, by using long mixing times to probe the large distances involved. These results suggest that the synthetic scope and utility of the cyanosilylation reaction remains to be more fully exploited.

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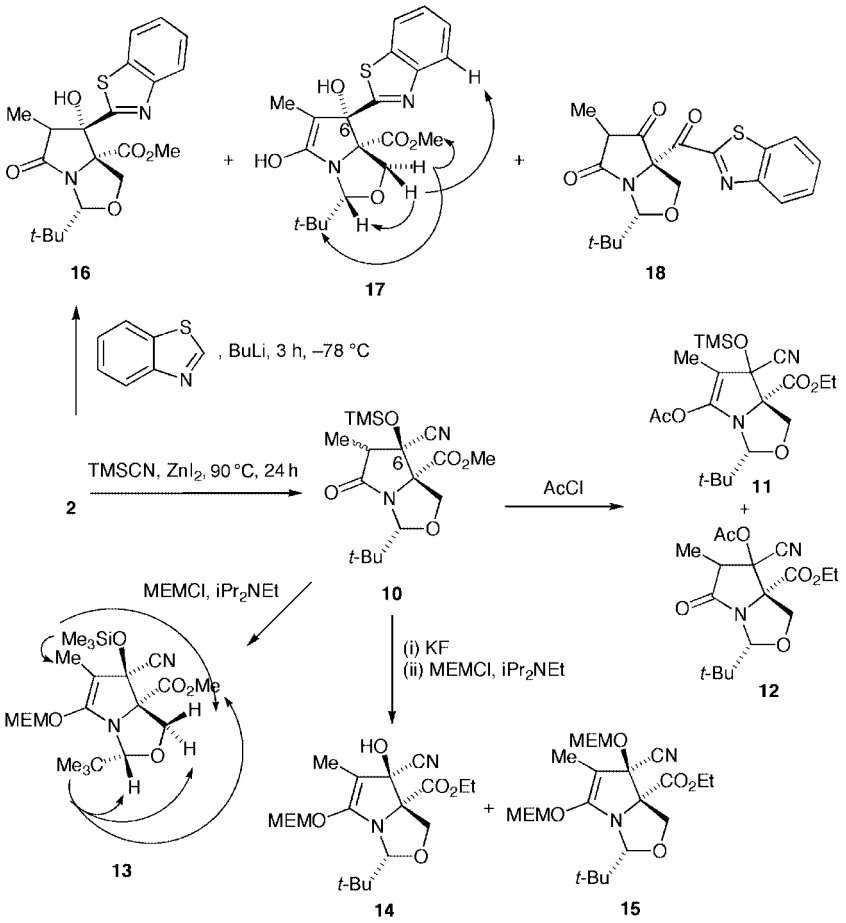

Scheme 4

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(19) A typical experimental procedure is as follows: to the ketone (2–3 mmol) was added freshly distilled TMSCN (3 equiv, distilled over CaH_2) and ZnI_2 (3–5 mg, dried over P_2O_5) and the mixture was stirred at r.t. (or 90 °C for tetramic acid **2**) for 24 h (6 h for compound **9**). The crude product was immediately purified by flash chromatography using a petroleum ether–EtOAc eluant.
(20) All new compounds gave satisfactory spectroscopic and high-resolution mass spectrometric or analytical data.
(21) These diastereomers were readily distinguishable by ^{1}H NMR spectroscopy: for **6a** at δ = 2.9 and 3.4 ppm (J = 13.6 Hz) and for **7a**, the benzylic resonances appeared as a dd at δ = 2.5 and 3.6 ppm (J = 13.2 Hz).
(22) The reaction of **5b** differs from the earlier cases, since it exists exclusively as the enol tautomer, and product **6b**/**7b** was not stable.
(23) Additional support for the fact that lactam **10** was epimeric at C-7 came from a consideration of ^{13}C NMR values: the ^{13}C nitrile resonances for the two disatereomers of **4a** were at δ = 120.16 and 118.99 ppm, for **4b** were at δ = 122.32 and 119.32 ppm, and for **6a** and **7a** were at δ = 119.08 and 118.86 ppm. For cyanohydrin **10**, the corresponding values were 114.8 and 114.9 ppm, and for the single diastereomers **11** and **13**, the values were 115.0 and 116.2 ppm.
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