

The reaction of TMS-CF₃ with amino acid derived ring-templates: studies with oxazin-2-ones and oxazolidin-5-ones

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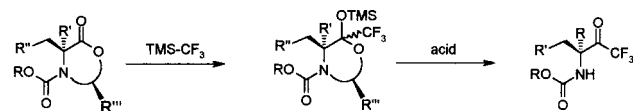
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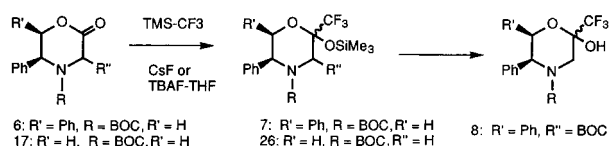
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The reaction of TMS-CF₃ with oxazin-2-ones and oxazolidin-5-ones and its dependency on steric factors was investigated.

(Trifluoromethyl)trimethylsilane (TMS-CF₃) is a convenient trifluoromethylating reagent which reacts with a variety of carbonyl compounds including ketones, aldehydes and five- or six-membered ring lactones.⁶ We have reported previously that reaction of TMS-CF₃ with amino acid derived oxazolidin-5-ones followed by mildly acidic hydrolysis gives access to biologically active *N*-substituted trifluoromethyl ketones.¹⁰



Here we describe the reaction of TMS-CF₃ with amino acid derived ring 'templates'. The work was carried out in the hope of developing a general stereoselective route to α -disubstituted trifluoromethyl ketones. We investigated the diastereoselective alkylation of suitable amino acid derived templates, such as oxazin-2-ones or oxazolidin-5-ones, followed by reaction with TMS-CF₃ to give highly substituted trifluoromethylated adducts (Scheme 1).



Oxazin-2-one **6** (Williams' template)³ with no substituents in the 3-position reacted smoothly with TMS-CF₃ using TBAF/THF as initiator to give the desired adduct **7** in good yield (82%) and in high diastereomeric excess (together with some desilylated material **8**) (Scheme 2). Complete desilylation was achieved using a stoichiometric amount of TBAF-THF or CsF with sonication. In this case, the stereochemistry at the newly formed stereo-centre (C-2) in **5** was determined to be *2S* by X-ray analysis (Fig. 1).¹⁶

Several substituted analogues of **6** were prepared following standard literature procedures and their reaction with TMS-CF₃ investigated.^{15,17} It was found that even a small substituent (methyl) in the 3-position led to poor yields (35% for methyl) of the trifluoromethylated adduct. Bulkier substituents (*e.g.* PhCH₂) prevented completely the addition of TMS-CF₃.

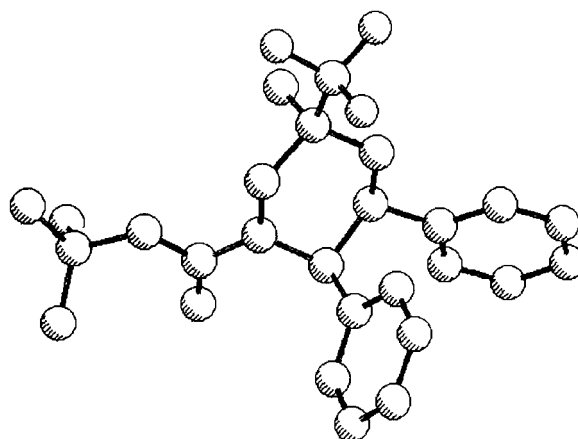
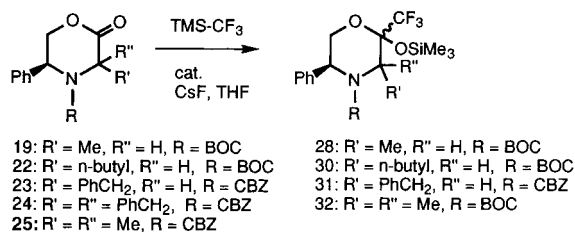


Fig. 1 View from the X-ray structure of **7**.

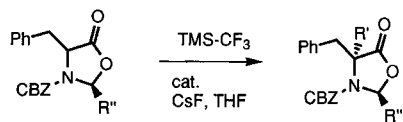
Further evidence for the importance of steric factors in the trifluoromethylation of oxazin-2-ones was obtained from addition of TMS-CF₃ to the less hindered monophenyl oxazin-2-one template **17** ('Dellaria's template')¹⁹ (Scheme 3). Here it was found that the addition of TMS-CF₃ occurred in the presence of a variety of different substituents in the 3-position, *e.g.* > 95% for reaction of **19**, R' = Me, R'' = H, R = BOC; >95% for reaction of **23**, R' = PhCH₂, R'' = H, R = CBZ; 76% for reaction of **22**, R' = *n*-butyl, R'' = H, R = BOC). However, the reaction was still susceptible to steric factors, *e.g.* whilst the dimethylated template (**25**, R' = R'' = Me, R = BOC) reacted to give an adduct **32** in 60%, the dibenzylated substrate (**24**, R' = R'' = PhCH₂, R = CBZ) did not give any of the desired product. In comparison with reactions of the Williams' template, as may be expected for the less hindered Dellaria



template, it was also observed that additions generally proceeded with lower diastereoselectivity (*ca* 30 to >95%).

Completion of the stereoselective approach to substituted trifluoromethyl ketones as outlined in Scheme 1 required efficient cleavage of the trifluoromethylated oxazin-ring. However, we were unable to achieve this using a variety of hydrolytic and hydrogenolytic reaction protocols.

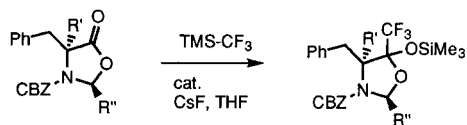
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R'' = C₆H₄-p-OMe or t-Bu

Scheme 4

The influence of steric effects on the addition of TMS-CF₃ was also investigated for C-4 di-alkylated oxazolidin-5-ones. The latter were prepared by alkylation of C-4 monosubstituted oxazolidin-5-ones using LHMDS as base (Scheme 4). As



2: R' = Me, R'' = C₆H₄-p-OMe
4: R' = Me, R'' = t-Bu

3: R' = Me, R'' = C₆H₄-p-OMe

Scheme 5

expected from the work of Seebach the alkylation reaction proceeded with excellent stereoselectivity.¹¹

We have previously shown that mono-alkylated analogues react generally in yields of >90% with the TBAF/THF initiator system. Reaction of TMS-CF₃ with disubstituted oxazolidin-5-ones, such as **2** was found to proceed sluggishly and gave **3** in poor yields (0–35%). The reaction required more vigorous conditions for initiation (CsF with sonication) (Scheme 5). Attempts to effect trifluoromethylation of *tert*-butyl substituted oxazolidin-5-one **4** with TMS-CF₃ failed

both with caesium fluoride/sonication and with TBAF-THF as initiator.

In summary we have shown that addition of TMS-CF₃ to amino acid derived ring templates is significantly dependent upon the steric environment of the carbonyl group. In the case of the 'less substituted' oxazin-2-ones and oxazolidin-5-ones the addition reaction occurs in moderate to good yields.

References: 22

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