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Synthesis and Reactivity of Pyrrolidinone- and Piperidinone-Derived Enol Triflates

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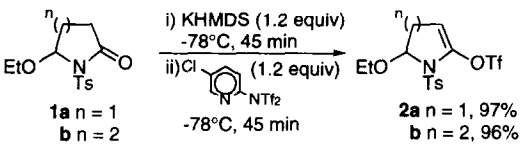
Abstract: A high yielding route to cyclic lactam-derived enol triflates is given along with a study of the structural features necessary for such triflates to be of useful thermal stability. Some Pd(0)-mediated coupling reactions are disclosed as well as the first functionalisation reactions of the double bond of the resulting enamide products. Copyright © 1996 Elsevier Science Ltd

The synthesis and reactivity of enol triflates derived from aldehydes and ketones has been thoroughly investigated over the last decade[1]. Such triflates undergo numerous coupling reactions which were recently reviewed[1]. This methodology has also been extended to triflates derived from lactones[2a] and thiolactones[2b].

There have been some problems, however, extending this methodology to the synthesis of lactam-derived triflates. Isobe reported the synthesis of an *N*-benzoyl-piperidinone-derived triflate (6-membered ring) and its subsequent coupling with an acetylene[3]. The pyrrolidinone-derived analogue (5-membered ring) was also prepared, however in moderate yield, and it could not be coupled due to its instability[3b]. Comins reported in detail some elegant methodology utilising piperidinone-derived triflates but he was unable to prepare the corresponding pyrrolidinone variants[4]. This year in a seminal publication we disclosed the preparation of an *N*-tosyl-pyrrolidinone-derived triflate, in moderate yield, and some palladium-catalysed coupling reactions[5].

In this communication we present a much improved synthetic route to lactam-derived enol triflates of both 5- and 6-membered ring sizes. We also give an insight into which structural features are necessary for a pyrrolidinone-derived triflate to be of useful stability. Some additional palladium-catalysed couplings are disclosed as well as the first functionalisation reactions of the double bond of the resulting enamide products.

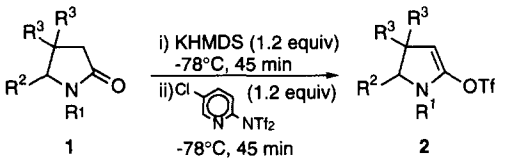
The initial substrate selected for enol triflate formation was the *N*-tosyl-α-ethoxypyrrolidinone (**1a**)[5] (**Scheme 1**). Our previous route to triflate (**2a**) (i KHMDS, -78°C, ii Tf_2O) was found to be somewhat capricious with yields varying and product decomposition a problem. We have now established that Comins' *N*-(5-chloro-2-pyridyl)triflimide[6] (**3**) efficiently traps the potassium enolate of (**1a**), affording the pyrrolidinone-derived triflate (**2a**) in a reproducible 97% yield on scales ranging from 20 mg to 2 g[7]. The use of KHMDS was essential in the enolate forming step, as the corresponding lithium enolate (from LiHMDS) did not react with (**3**). The purity of (**3**) was crucial in obtaining these high yields (commercial samples of (**3**) required Kugelrohr distillation before use). Application of these standard conditions to the corresponding 6-membered *N*-tosyl-lactam[8] (**1b**) gave a similarly high yield of the piperidinone-derived triflate (**2b**)[9].



Scheme 1

Triflate (**2a**) in neat form, was stable only for short periods of time (*ca.* 10 min) at room temperature (decomposition pathway involved EtOH elimination, affording a pyrrole). It could be stored at -20 °C for a month without degradation, and handled as a dichloromethane solution at room temperature without problems. Triflate (**2b**) was considerably more stable, surviving for extended periods (over 3 months) at -20 °C, and for hours at room temperature. With a reliable route to *N*-tosyl-pyrrolidinone-based triflates in hand, we turned our attention to a study of the structural features influencing their thermal stability.

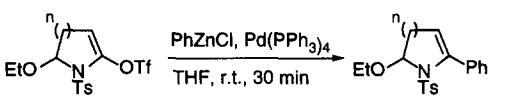
Three additional pyrrolidinones (**1c-e**)[8] were selected for attempted triflate formation (**Scheme 2**). Triflate (**2c**) derived from *N*-tosyl-2-pyrrolidinone (**1c**), devoid of the ethoxy group, was formed quantitatively under the standard conditions (^{1}H-NMR: δ 5.12 (1H, t, J = 3.0 Hz, alkenyl-H)). It was less stable than (**2a**) and decomposed immediately following chromatography, conclusively illustrating the stabilising influence of the α-ethoxy group. All attempts to prepare triflate (**2d**), containing the ethoxy group, but with an *N*-*t*-butoxycarbonyl (BOC) substituent rather than an *N*-tosyl completely failed, indicating the need for a strongly electron withdrawing group on the nitrogen. This is in line with the comments of Isobe[3] and Comins[4] who find *N*-benzoyl analogues highly unstable. Finally, the more highly substituted triflate (**2e**) could be synthesised in excellent yield, although an inverse addition technique was necessary to quantitatively form the initial potassium enolate (*i.e.* add (**1e**) to KHMDS). This result was pleasing as we eventually hope to synthesize enantiopure triflates from the corresponding *N*-tosyl-pyrrolidinones[10] bearing substituents at C4. The two methyl groups were intended to increase the stability of the triflate product by inhibiting the possibility of pyrrole formation *via* EtOH elimination. Surprisingly, (**2e**) was found to be of similar stability to (**2a**), affording starting material after standing at room temperature.



	Compound 1 / 2 R^1	R^2	R^3	Yield % Isolated (crude)
a	Ts	OEt	H	97 (100)
c	Ts	H	H	0 (100)
d	BOC	OEt	H	0 (0)
e	Ts	OEt	Me	90 (100)

Scheme 2

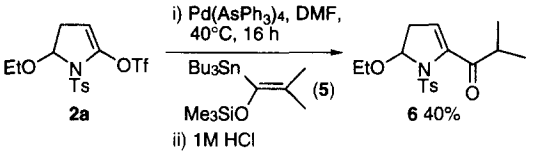
Due to the limited thermal stability of the pyrrolidinone-based triflates, the search for productive coupling reactions proceeding under mild conditions was viewed as essential in establishing them as useful synthetic intermediates. Some palladium catalysed coupling reactions of (**2a**) were recently disclosed[5]. However, there still remained some problems to be solved. For example, the palladium-catalysed arylation of (**2a**) with phenyltributyltin proceeded in poor yield (38% yield, 56% based on recovered starting material) after extended reaction times. The analogous coupling with phenylzinc chloride[11] (prepared *in situ* from PhLi and $ZnCl_2$) was found to be far superior, occurring in excellent yield after only 30 min at room temperature allowing the efficient incorporation of an aromatic substituent (**Scheme 3**). Unfortunately, coupling with alkylzinc chlorides and iodides did not proceed as desired, affording only protonation products consistent with a β-hydride elimination step in the catalytic cycle[12].



Scheme 3

The couplings of (**2a**) with vinyltributyltin and 2-(ethoxy)-vinyltributyltin have been documented[5]. We were interested in extending the scope of these mild Stille couplings to include more hindered stannanes. Triflate (**2a**) was successfully coupled with stannane (**5**)[13], affording (**6**) in moderate yield, accomplishing the one-pot incorporation of the isobutanone unit (**Scheme 4**). The yield reflects the problematic product isolation ((**2a**), (**5**) and (**6**) are of almost identical polarity and limited stability) rather than the smoothness of the

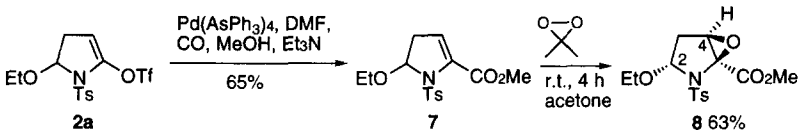
coupling reaction. This is the first successful Stille coupling of (**5**) to occur under mild conditions (the only previous coupling, with an aryl bromide, occurred at 110°C in a similar yield[13]), and the first with a vinyl triflate.



Scheme 4

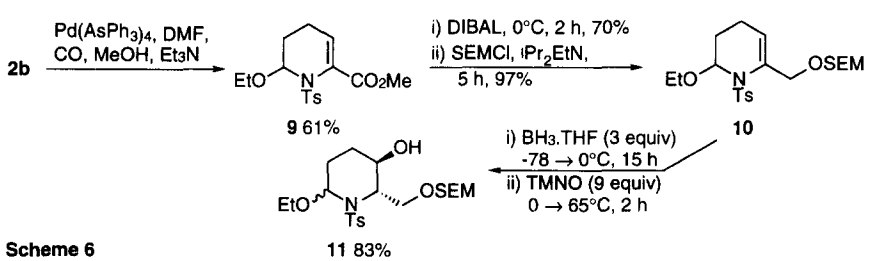
The coupling products available from pyrrolidinone- and piperidinone-derived triflates all contain an enamide moiety for further functionalisation. Comins has reported the enantioselective hydrogenation of a similar piperidinone-derived enecarbamate[4]. However, the functionalisation of substituted *N*-tosyl-enamides is, to the best of our knowledge, unknown.

We were encouraged by recent reports documenting the epoxidation of electron poor olefins using dimethyldioxirane[14]. A suitable substrate (**7**) was prepared from triflate (**2a**) as previously described[5] (**Scheme 5**). This reacted smoothly with an acetone solution of the dioxirane at room temperature to afford the sensitive epoxide (**8**) in good yield, interestingly as a single diastereomer[15]. Epoxide (**8**) was tentatively assigned as the isomer indicated due to the lack of an NOE between H2 and H4. Work is in progress to elucidate the synthetic utility of this novel epoxide.



Scheme 5

There have been only three reports documenting the hydroboration of cyclic ene-carbamates and -amides[16] (all disubstituted). The analogous reactions of trisubstituted *N*-tosyl-enamides have not been investigated. Triflate (**2b**) was reacted with CO and methanol under Pd-catalysis[1] to afford methyl ester (**9**) (**Scheme 6**). This enamide containing an extremely electron-poor olefin was, not surprisingly, inert to hydroboration. Reduction of the ester, followed by protection as the SEM ether gave (**10**) in excellent yield, which was used as a substrate to screen suitable hydroboration reactions. After several optimisation studies it was eventually found that hydroboration with borane.THF occurred at a reasonable rate at temperatures >-10°C, and the resulting borane intermediate was only stable at 0°C or below. Oxidative work up with hydrogen peroxide gave complex product mixtures, however oxidation with trimethylamine-*N*-oxide[17] afforded the desired alcohol (**11**) in 83% yield, as a 15 : 1 mixture of (unassigned) diastereomers. The excellent diastereoselectivity observed is in contrast with previous efforts on enecarbamates[16a,b], and has promising implications for natural product synthesis.



Scheme 6

In conclusion, we have demonstrated that both pyrrolidinone- and piperidinone-derived enol triflates are accessible in almost quantitative yields by a judicious choice of substituents. The new elaboration reactions presented compliment previous efforts[4,5], with a mild arylation procedure using organozincs being noteworthy. Although previously thought relatively inert[18], we have shown for the first time that the *N*-tosyl-enamide olefin will undergo both epoxidation and hydroboration. The combination of these results goes some way to establishing lactam derived enol triflates as powerful intermediates for organic synthesis.

Acknowledgments: we thank the Royal Society (Science Exchange Fellowship) and the European Union (TMR fellowship) for generous financial support.

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7) To a stirred solution of lactam (**1a**) (0.200 g, 0.706 mmol) in THF (6 mL) at -78 °C under nitrogen was added KHMDS (1.7 mL of a 0.5 M solution in toluene, 0.85 mmol, 1.2 equiv), and the pale yellow solution stirred for 45 min. A solution of (**3**) (0.332 g, 0.845 mmol, 1.2 equiv) in THF (0.7 mL) was added rapidly in one portion. After stirring for 45 min the reaction was warmed to 0 °C. Saturated ammonium chloride solution (5 mL) followed by dichloromethane (8 mL) and water (5 mL) were added and the organic layer separated. The aqueous layer was extracted with dichloromethane (5 mL) and the combined organic solutions dried (Na_2SO_4) and the solvent removed *in vacuo*. Column chromatography (20 → 50% dichloromethane in light petroleum ether, on SiO_2) afforded triflate (**2a**) as a colourless oil (0.276 g, 97%). Data as previously reported[5].
8) All *N*-tosyl lactams were prepared from the corresponding lactams (i) n-BuLi, -78 °C, 1 h; (ii) TsCl, -78 °C (2 h) → r.t. (12 h). For lactam precursors (**1a**) and (**1b**): Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437; (**1e**): Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179.
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15) Only one isomer detected by ^{1}H-NMR: δ 7.897 (2H, d, J = 8.3 Hz, **Ts**), 7.310 (2H, d, J = 8.1 Hz, **Ts**), 5.063 (1H, dd, J = 6.4, 1.7 Hz, **H2**), 3.914 (1H, d, J = 3.4 Hz, **H4**), 3.887 (3H, s, O**Me**), 3.715 (1H, dq, J = 9.4, 7.1 Hz, O**CH$_2$**Me), 3.449 (1H, dq, J = 9.4, 7.0 Hz, O**CH$_2$**Me), 2.433 (3H, s, **Ts**), 2.309 (1H, dd, J = 15.2, 6.3 Hz, **H3**), 2.097 (1H, ddd, J = 15.2, 3.3, 2.3 Hz, **H3**), 1.112 (3H, t, J = 7.0 Hz, OCH$_2$**Me**).
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