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The First Examples of Nazarov Cyclizations Leading to Annulated Pyrroles

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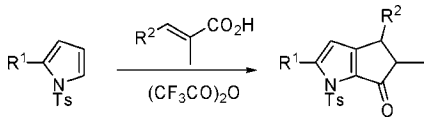
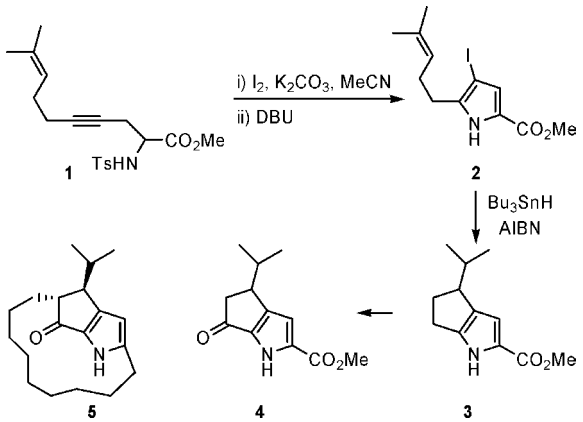
ABSTRACT



Reactions between α-substituted unsaturated carboxylic acids 20 and *N*-tosylpyrroles [14, 23] in the presence of trifluoroacetic anhydride result in smooth α-acylation of the pyrrole, followed by Nazarov cyclization to give 50–80% yields of cyclopenta[*b*]pyrroles. The presence of an α-substituent in the unsaturated acid appears to be mandatory.

Of the many methods available for the synthesis of conjugated cyclopentenones, such as intramolecular aldol condensations[1] or Pauson−Khand reactions,[2] the Nazarov cyclization[3] is distinguished by the fact that the 3,4-C−C bond of the new ring is formed during one of the key steps. We have recently developed a novel approach to the cyclopentapyrrol-6-one **4** (Scheme 1),[4] related to the more complex structure **5**, a synthetic precursor of the natural product Roseophilin.[5] Our primary aims during this endeavor were to demonstrate that our 5-*endo*-dig/elimination strategy for the synthesis of 4-iodopyrrole-2-carboxylates[6] was compatible with potentially reactive unsaturated side chains and that the resulting iodopyrroles [e.g., **2**] could provide well-behaved radicals, which would undergo subsequent cyclizations, leading in this case to the cyclopentapyrrole **3**. Subsequent oxidation would then provide the target ketone **4**. While this approach worked well, it did require a relatively large number of steps. We realized that, if the ketone **4** were to be regarded as a cyclopentenone derivative **6**, then a

Scheme 1. An Approach to the Core of Roseophilin **5**



(1) For recent contributions, see: Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766. Keranen, M. D.; Eilbracht, P. *Org. Biomol. Chem.* **2004**, *2*, 1688. Zheng, Y. S.; Avery, M. A. *Tetrahedron* **2004**, *60*, 2091.

(2) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castelles, J. *Chem. Soc. Rev.* **2004**, *33*, 32. Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800.

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(5) For a comprehensive review, see: Furstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582.

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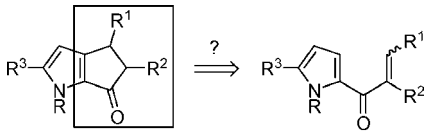
shorter synthesis could feature Nazarov cyclizations of the enones **7** (Scheme 2).

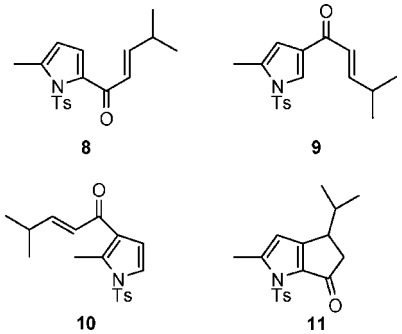
Scheme 2. A Possible Nazarov Cyclization of Ketopyrroles



6 **7**

We further reasoned that the enamine-like character of the pyrrole nucleus should contribute positively to such cyclizations, given that we could identify a suitable attenuating group ("R" on nitrogen), which would confine this reactivity to a controllable level. To our surprise, we could find no previous examples of Nazarov cyclizations involving pyrroles, although a single example of this type of reaction featuring an indole has been described.[7]

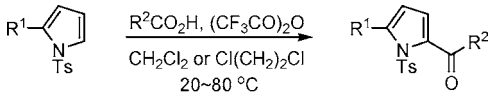
In initial experiments, we identified a possible reason for this. The model substrate **8** was prepared from the corresponding saturated ketone[8] by sequential selenenylation [LDA, −78 °C, THF, PhSeCl] and oxidation. However, exposure of this compound to a wide range of both Brønsted and Lewis acids under a variety of conditions usually resulted in no reaction or complete decomposition. At best, mixtures of the ketone **8**, the two isomeric ketones **9** and **10**, presumably products of a *retro*-Friedel−Crafts acylation and re-acylation, and finally the desired product **11** were formed in relatively similar amounts when using tin(IV) chloride in chloroform at ambient temperature. As the synthesis of precursor **8** also proved to be somewhat capricious and inefficient, we were left with a splendidly brief approach consisting of only three steps to our target **11**, but in an unacceptably low overall yield of less than 10%. However, the full potential of this tantalizing result was brought into focus by our discovery of a superior method for the direct acylation of *N*-tosylpyrroles with carboxylic acids.[8] Herein, we report the successful development of a tandem acylation/Nazarov cyclization protocol, based on this methodology and also some surprises, which helped to define the probable mechanism of the Nazarov step.



8 **9** **10** **11**

The key was our finding that trifluoroacetic anhydride is an excellent reagent for achieving the direct acylation of *N*-sulfonyl pyrroles **12** by carboxylic acids (Scheme 3).[8]

Scheme 3. Direct Acylation of *N*-Tosylpyrroles

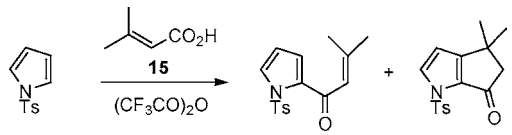


12 **13**

Yields of pyrryl ketones **13** are usually excellent: highly significant, especially in view of the foregoing model results, is that the method is essentially regiospecific, in favor of the α-isomers. We therefore applied this new method to unsaturated carboxylic acids, in the hope that the initial acylation might be followed by a Nazarov cyclization, if we were to add a suitable trigger. In the event, this latter tactic proved unnecessary.

The first attempts with *N*-tosylpyrrole **14** and 3,3-dimethylacrylic acid **15** showed promise (Scheme 4).

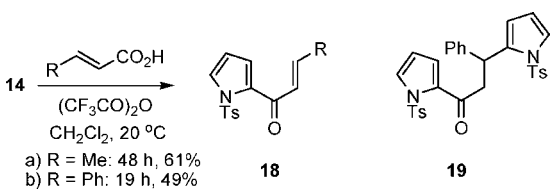
Scheme 4. Sequential Direct Acylation and Annulation with 3,3-Dimethylacrylic Acid



14		**16**	**17**
	CH_2Cl, 20 °C, 48 h	63%	13%
	$Cl(CH_2)_2Cl$, 80 °C, 16 h	0%	51%

Prolonged reaction at ambient temperature gave the acylation product **16**, along with some of the cyclopentapyrrole **17**, the yield of which was increased to around 50% when the entire reaction sequence was carried out in refluxing dichloroethane. The use of even higher boiling halocarbons such as chlorobenzene proved to be too vigorous and (product) decomposition occurred. However, all attempts to generate similar products from either crotonic or cinnamic acid failed and only the acylation products **18** were isolated (Scheme 5), along with traces of the Michael adduct **19** in

Scheme 5. Acylation but No Nazarov Cyclization with Crotonic and Cinnamic Acids



a) R = Me: 48 h, 61%
b) R = Ph: 19 h, 49%

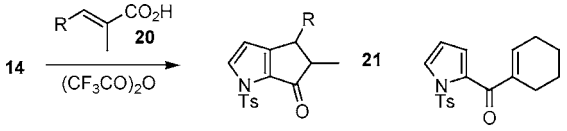
18 **19**

the case of the latter acid. More vigorous conditions again resulted in extensive decomposition/polymerization.

It was only when we turned to α-substituted unsaturated carboxylic acids **20** that the two consecutive steps again

began to take place and respectable yields of the cyclized products **21** were obtained under a variety of conditions (Scheme 6). Not surprisingly, the trans isomers were the

Scheme 6. Sequential 2-Acylation and Nazarov Cyclization of *N*-Tosylpyrrole



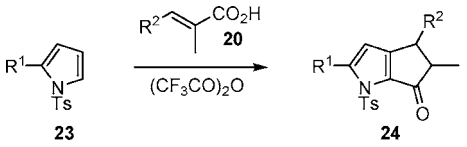
a) R = H: $Cl(CH_2)_2Cl$, 80 °C, 19 h, 73%.
b) R = Me: CH_2Cl_2, 20 °C, 68 h, 59%, 2:1 *t*/*c*.
c) R = Ph: CH_2Cl_2, 40 °C, 40 h, 50%, 6:1 *t*/*c*.

major products, which were identified by their relatively smaller coupling constants [$J_{4,5} \approx 2-3$ Hz]. The corresponding cis isomers show $J_{4,5} \approx 5$ Hz.[9] One extrapolation too far was an attempted tandem reaction with 1-cyclohexenecarboxylic acid, which gave only the acylated pyrrole **22** (72%) at ambient temperature; once again, at higher temperatures, decomposition occurred

In general, a longer reaction time at a lower temperature gave slightly better yields than shorter reaction times at higher temperatures, when using 2−3 equiv of the carboxylic acid and an excess of trifluoroacetic acid.

The presence of an α-methyl group also allowed smooth cyclization to take place with 2-substituted pyrroles **23** (Scheme 7). The presence of an electron-donating 2-methyl

Scheme 7



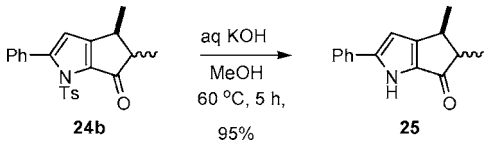
a) $R^1 = R^2$ = Me: CH_2Cl_2, 20 °C, 48 h, 77%, 6:1 *t*/*c*.
b) R^1 = Ph, R^2 = Me: CH_2Cl_2, 40 °C, 96 h, 51%, 6:1 *t*/*c*.
c) R^1 = Me, R^2 = H: $Cl(CH_2)_2Cl$, 80 °C, 21 h, 82%.
d) R^1 = Me, R^2 = ^{i}Pr: CH_2Cl_2, 20 °C, 48 h, *t* only, 64%.

group on the pyrrole nucleus, quite reasonably, was observed to speed up the transformation overall while, conversely, a 2-phenyl group slowed the process, presumably by reason of its electron withdrawing effect. Lack of a β-substituent in the carboxylic acid again meant (cf. Scheme 6) that relatively more forcing conditions were required to secure the final product **24c** in reasonable yield. Further, in this case, there was some loss of regioselectivity and a small amount (ca. 9%) of the product arising from β-acylation was isolated.

Finally, the product **24d**, of possible relevance to Roseophilin synthesis,[5] was isolated in good yield (64%) as a single trans isomer (Scheme 1),[9] presumably a reflection of the bulk of the isopropyl group and also consistent with the formation of mixtures, albeit ones highly biased [6:1] in favor of the trans isomers, when the substituent groups were smaller [**24a**,**b**].[10] Overall, this combination of reactions is very simple to perform and highly reproducible, without the need for any special precautions, beyond using clean, dry reagents.

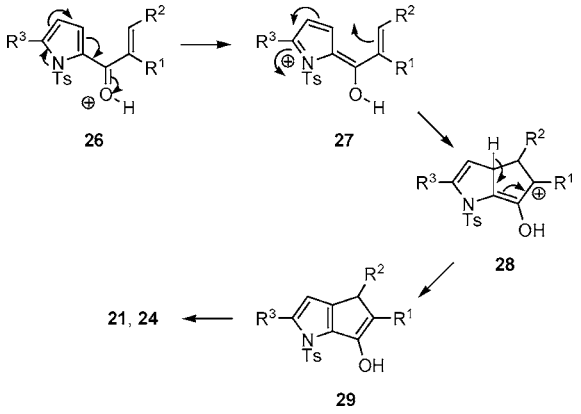
Free ketopyrroles [e.g., **25**] could be obtained by base hydrolysis of the tosyl group in excellent yields, without altering this isomer ratio, indicating that the initially isolated products are probably the thermodynamic mixtures (Scheme 8).

Scheme 8. Generation of a Free Pyrrole



The finding that an α-substituent in the carboxylic acid component was necessary for the success of the Nazarov step rather suggests that the generally accepted mechanism[3] of this cyclization is in operation. Thus, protonation of a generalized unsaturated ketone, presumably by the trifluoroacetic acid formed during the acylation step,[8] would generate the oxonium ion **26**, which should be in equilibrium with the iminium species **27** (Scheme 9). A subsequent

Scheme 9. Suggested Mechanism



Nazarov ring closure which, although indicated as a concerted process in Scheme 9, could well feature resonance to a pentadienyl carbenium ion followed by a conrotatory ring

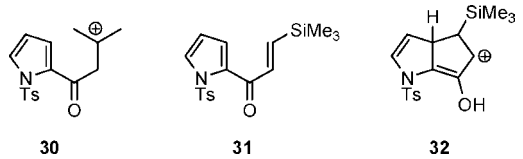
(7) Cheng, K. F.; Chan, K.-P.; Lai, T.-F. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2461.
(8) Song, C.; Knight, D. W.; Whatton, M. A. *Tetrahedron Lett.* **2004**, *45*, 9573.
(9) For a recent example, see: Robertson, J.; Menard, M.; Ford, R.; Bell, S. *Org. Biomol. Chem.* **2004**, *2*, 2988. This was also consistent with the observed relative upfield shift (ca. 0.5 ppm) of the methine protons at the ring branches of the trans isomers when mixtures were obtained; see: Anteunis, M.; Dannels, D. *Org. Magn. Reson.* **1975**, *7*, 345.
(10) Full spectroscopic and analytical data consistent with all the proposed structures have been obtained for all compounds reported herein.

closure, would then lead to the bicyclic framework, crucially having a tertiary carbenium ion **28** only when there is an α-substituent (R^1) present in the initial carboxylic acid. Proton loss would then lead to the neutral enol **29**, tautomerization of which would finally give the observed products **21** and **24**.

Chemical semantics perhaps, but this pathway does appear to explain what a number of alternative mechanisms seemingly cannot. Steric arguments seem less relevant, as the conformations of the precursors necessary for reaction appear to be those with the least degree of steric crowding.

By contrast, formation of the dimethyl derivative **1**7 from 3,3-dimethylacrylic acid **15** (Scheme 4) may be a more straightforward Friedel−Crafts alkylation involving the tertiary carbenium ion **30**. Overall, however, the mechanism may be somewhat more subtle, as trifluoroacetic acid was *not* a successful trigger of the Nazarov cyclization when applied to an isolated unsaturated pyrryl ketone. Further, it has been very well established that the well-known ability of trimethylsilyl groups to stabilize carbenium ions β to them can be highly influential in facilitating Nazarov cyclizations.[3] Unfortunately, we found that 3-trimethylsilylacrylic acid[11] failed to react cleanly with *N*-tosylpyrrole to give the ketone **31** (Figure 1). Had it done so, we would anticipate that the trimethylsilyl group could have compensated for the absence of a stabilizing substituent in the putative carbenium ion intermedate **32**.

In the absence of a successful initial acylation, this will have to remain a moot point. In any event, this method represents a useful and rapid protocol for the cyclopentannelation of pyrroles, which should be compatible with at least some other functional groups, such as esters or remote alkenes.



30 **31** **32**

Figure 1. Possible intermediates.

While this paper was in preparation, an Italian group reported that various *N*-tosyl dihydropyrroles also undergo this type of Nazarov cyclization.[12] Returns from the key step are comparable to the foregoing, but the additional step required to reach the pyrrole oxidation state with use of DDQ is somewhat inefficient.

Acknowledgment. We are grateful to the EPSRC Mass Spectrometry Service, University of Swansea, for the provision of high resolution mass spectrometric data and the EPSRC for partial financial support.

Supporting Information Available: Typical experimental procedures and spectroscopic and analytical data for compounds **17**, **21**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 3975.

(12) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542.