Novel Class of Morphinans with Acrylonitrile Incorporated Substructures as Key Intermediates for Non-Oxygen-Bridged Opioid Ligands

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With increasing knowledge about agonistic and antagonistic activities of morphinan derivatives, the field of potential applications for this class of compounds is broadening, and the demand of novel substitution patterns is rising. Among the most indispensable analgesics, the structural analogues of 6-ketomorphinans are of main importance both in clinical use and as pharmacological tools.[1] As recently shown, hydrazones, oximes, carbazones, and semicarbazone derivatives of 6-ketomorphinans, like dihydromorphinone or oxymorphone, exhibit a high affinity at the μ-opioid receptor binding site.[2−4] Since most of these compounds show a high antinociceptive potential in addition to lower side effects,[5,6] it remains a promising synthetic task to convert the carbonyl group into various functionalities.

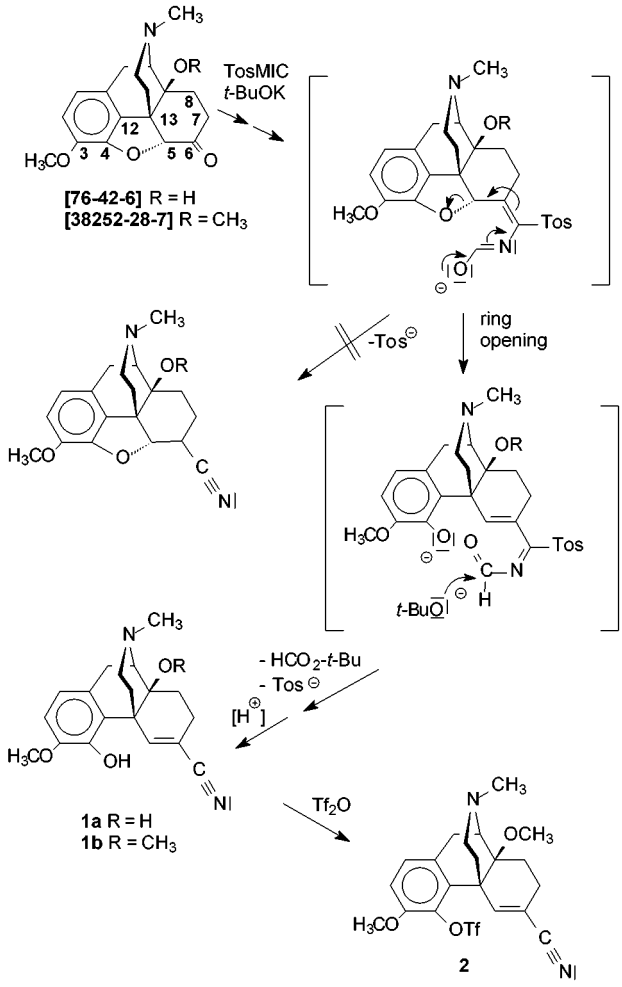
An interesting approach in this regard is the van Leusen homologisation reaction in which the standard reagent tosylmethylisocyanide (TosMIC) reacts with carbonyl compounds to give the corresponding nitriles with one additional carbon atom.[7]

This methodology is well established. However, in contrast to reports about similar systems published so far,[7] the actual reaction pathway of the key step in the present system appears to deviate from the expected mechanism.

Starting from the 6-ketomorphinans, oxycodone [Registry No. 76-42-6] and 14-*O*-methyloxycodone [Registry No. 38252-28-7], the expected carbonitriles are not obtained. Instead, the ether bridge between positions 4 and 5 of the starting compound is opened and the respective acrylonitrile derivatives **1a** and **1b** are formed exclusively (Scheme 1).[1]

The concomitant specific scission of the oxygen bridge between positions 4 and 5 provides a high synthetic synergism with regard to combinatorial diversity. That holds true especially for intramolecular reactions such as ring reclosures and ring expansions. This is an additional advantage since most methods for carbon−oxygen ether cleavage require harsh reaction conditions such as mineral acids, boron trihalides, or thiolates. These preparative limitations also apply to morphinan chemistry,[8−10] thus leading to unspecific conversions and byproducts. Reductive methods which are commonly used for selective ring opening reactions in morphinan chemistry[11] bear the imminent disadvantage of an undesired defunctionalization of position 5 yielding a synthetically less valuable hydrocarbon node.

Scheme 1. Modified van Leusen TosMIC Reaction with Concerted Ring Opening



The above-mentioned bridge reconstitutions provide access to hitherto unknown hetero- and carbocyclic systems as alternatives to the benzofuranic substructure of the morphinan progenitors.[12] Due to the specific reactivity of these systems they are uniquely capable of facilitating these bridge reconstitutions, for example, with *ipso* substituent groups and the acrylic coreactant as Michael acceptor, or as substrate for olefinic additions.

The required *ipso* substitutions necessitate previous phenol activation. This was exemplarily achieved by triflation of the selectively opened 4,5-oxygen bridge in compound **2** (Scheme 1). The ease of the triflation reaction is explainable by the absence of steric hindrance as is obvious from in the X-ray structure in Figure 1. The related organometallic morphinan chemistry has already been demonstrated successfully at the free phenolic moiety in position 3[13] resulting in heteroelement bioisosters, such as

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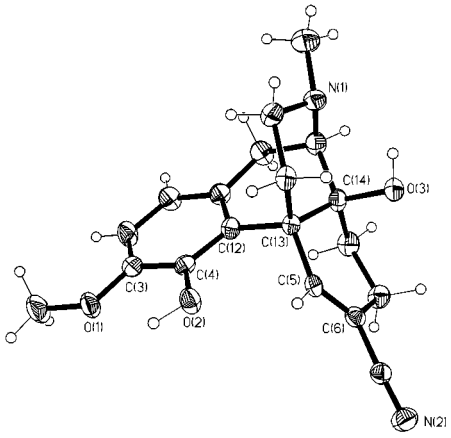

Figure 1. X-ray structure of **1a**.

3-sulfonamido analogues,[14] as well as 3-carbon functionalized morphinans with aryl, vinyl, methyl,[15] or cyano substituents.[16] In addition, the recently developed aromatic aminations mediated by transition metal catalysts[13,17] offer a more direct route to the target structures.

The acrylonitrile substructure itself holds promise for a separate subsequent chemistry. To be mentioned in this respect are transformations to aldehydes, conjugate cuprate additions,[18,19] hydrogenolysis, hydrolysis, hydrazinolysis, cycloadditions, and the like.

The construction of acrylonitriles under ring retainment is achievable by Pd-catalyzed cyanation of the receptive vinyl-triflates preformed from 6-ketomorphinans. However, this would result in the olefinic double bond located between positions 6 and 7, due to the preferred formation of the 6/7 enolate.[20] Thus, the Michael acceptor would be introduced apart from the phenolic position 4.

The follow-up chemistry based on the first examples presented herein will be the subject of a future publication.

The new synthetic concept is extraordinarily efficient and produces high yields within extremely short reaction times.

The reactions were carried out at 0 °C in DME, employing 1 equiv of *t*-BuOH, 1.3 equiv of TosMIC, and 2.6 equiv of *t*-BuOK. Under these conditions the reaction went to completion within a few minutes and the products **1a** and **1b** were isolated in excellent yields. The surprisingly rapid conversion and the unexpected products gave first evidence that obviously in the final step the reaction pathway differs from the regular mechanism established by van Leusen et al.[7]

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Scheme 2. Confirmed Intermediates[7] Found in the Authentic van Leusen TosMIC Reaction

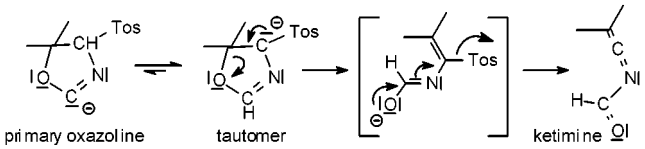

Table 1. Interatomic Angles of the 4/5 Ether-Bridged Oxycodone [Registry No. 76-42-6] (Scheme 1) Compared to the Ring-Opened Compound **1a** (CCDC 159577)

interatomic angles	oxycodone·HCl values[a]	theoretical values	**1a** values (ring open)
O(2)/C(4)/C(12)	111.6	120.0[b]	120.6
C(4)/C(12)/C(13)	109.2	120.0[b]	121.3
C(12)/C(13)/C(5)	98.2	109.5[c]	112.9
C(13)/C(5)/O(2)	104.5	109.5[c]	
C(3)/C(4)/O(2)	127.4	120.0[b]	118.6

[a] X-ray data from Cambridge CDC.[21] [b] sp^2-angle. [c] Tetrahedron angle.

In the first step, the TosMIC anion generated in situ forms a primary oxazoline intermediate[7] after a nucleophilic addition to the carbonyl carbon in position 6. The tautomer undergoes a oxazoline-ring opening sequence to form a (transient) formamide anion. Up to this stage the reaction mechanism is confirmed by the isolation of corresponding derivatives of the intermediates in related systems.[7]

The specific mechanistic deviations operative for the present system are explainable by the structural features of the morphinan molecule. Van Leusen et al. propose the formation of an intermediary *N*-formylketenimine (Scheme 2). Deformylation with *t*-BuOK followed by protic quenching of the resulting anion was expected to produce a carbonitrile that was not formed. Rather, the ring open structures **1a,b** were isolated as sole products (Scheme 1).

By the proposed mechanism the formation of the ketimine intermediate is skipped in favor of the direct formation of the conjugatively stabilized acrylonitrile. This mechanism involves the scission of the ether bridge still present in the oxazoline intermediate in one step (Scheme 1).

Complementary to the 4-phenolate leaving group ability, the major driving force of the concerted ring opening with its high reaction rate is attributable to the structural strain imposed by the ether bridge on the rigid polycyclic morphinan backbone. An indication for this strain is the considerable deviation of the angular values from the ideal angles (Table 1).

It can be concluded that the TosMIC reaction employed for morphinans is not only capable of opening a new area in opiate research, but also proves to be a powerful synthetic tool of general applicability.

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Supporting Information Available: Experimental procedures and spectral data and crystal data and structure refinement details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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