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Direct Room-Temperature Lactonisation of Alcohols and Ethers onto Amides: An "Amide Strategy" for Synthesis

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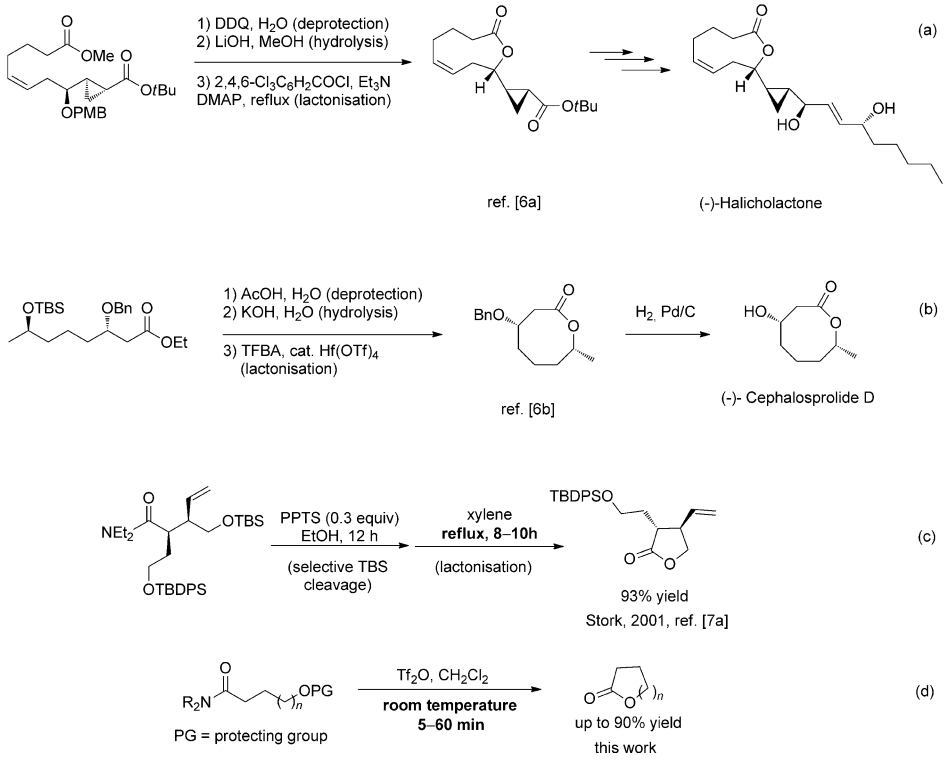
The amide functional group is usually considered as the most robust and resistant of the carboxylic acid derivatives. As taught in standard organic chemistry undergraduate textbooks, the reduced electronegativity of the nitrogen atom in an amide (as compared to oxygen in esters or acids) results in more effective orbital overlap with the adjacent carbonyl, thus markedly reducing its electrophilic character.[1] Therefore, it is not surprising that amide hydrolysis is a difficult transformation, which typically proceeds with notoriously long reaction times ($t_{1/2}$ of $>10^2$ years at pH 7 and 25 °C in aqueous solution).[2] Many elegant strategies have been developed to prepare so-called "twisted" amides, for which the aforementioned resonance stabilisation is greatly reduced by carefully designed strain elements[1a] and which have carbonyl reactivities akin to ketones.[3] On the other hand, lactones form structural units within a large range of naturally occurring biologically active compounds, and many methods of lactone preparation have gained relevance over the past few decades.[4] Nevertheless, the chemical synthesis of lactones of all ring sizes still relies predominantly on ring-closure techniques starting from ω-hydroxycarboxylic acids (seco-acids), esters or their activated derivatives, as evidenced by their prevalent use in the late stages of total synthesis efforts. Interestingly, in these strategies lactonisation is subordinate to two, often sequential, unproductive deprotection steps[5] for both the alcohol and the carboxylic acid moieties prior to the actual lactonisation event, as exemplified by the selected examples shown in Scheme 1 a,b.[6]



Scheme 1. Classical lactonisation strategies in multi-step synthesis (a,b). Thermal lactonisation of hydroxyamides (c) and room-temperature lactonisation of protected amidoethers (d). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-(dimethylamino)pyridine, TFBA = 4-(trifluoromethyl)benzoic anhydride, Tf = trifluoromethanesulfonate, PPTS = pyridinium-*p*-toluenesulfonate.

We herein report a new methodology for the formation of lactones directly from a protected alcohol and an "amide-masked" carboxylic acid (Scheme 1 d), which proceeds in a single step under mild conditions. To the best of our knowledge, lactonisations of this type have not been systematically explored in the literature and usually require rather harsh conditions, as exemplified by an early thermally induced γ-lactonisation key-step in Stork's landmark enantioselective

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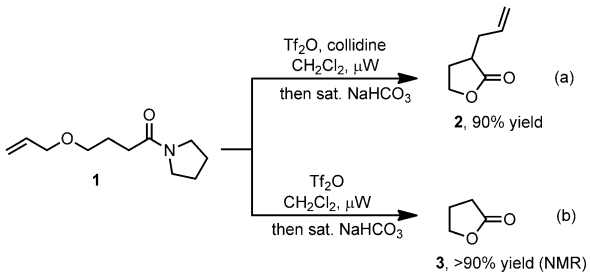
total synthesis of quinine (Scheme 1c).[7] The method described in this manuscript, in contrast, proceeds at room temperature over a few minutes.

Our group has previously reported an unexpected Claisen-like rearrangement of keteniminium salts that allows a stereoselective entry to challenging substituted α-allyl/allenyl/aryl lactones (Scheme 2a).[8]



Scheme 2. Claisen rearrangement of allyloxyamide **1** (a) and unexpected dealkylative lactonisation in the absence of base (b).

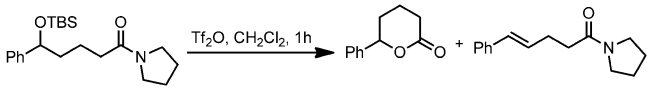
In the course of our studies on this reaction, we were surprised to observe the exclusive formation of α-unsubstituted, deallylated γ-lactone product **3** by treatment of the starting ω-allyloxyamide **1** with triflic anhydride in the absence of collidine (Scheme 2b).

This unexpected outcome presaged opportunities for the development of a new lactonisation strategy, which would proceed directly from a protected alcohol onto otherwise inert, stable amides. The attainment of such a goal would effectively bypass the need for the two sequential deprotection steps mentioned above, because both the hydroxy and the carboxy moieties' protection would actually be a crucial feature of the process.

Realising that the allyl moiety on substrate **1** might be replaced by other protecting groups, we initially turned our attention to the use of secondary alcohols bearing several different protecting groups (such as various silyl derivatives, acetals, benzyl derivatives and trityl among others).[9] We observed that all substrates studied were rapidly consumed in relatively short reaction times (between 5 min and 1 h) at room temperature to give the lactone along with variable amounts of an elimination by-product. Substrates bearing a benzylic secondary ether were found to be the most challenging in terms of competition between the formation of these two products. In our initial investigations, higher yields of lactone were obtained when *tert*-butyldimethylsilyl (TBS) was used as protecting group. Thus, we chose compound **4d** as a model substrate to gauge how to efficiently promote lactonisation (Table 1).

After screening different solvents and concentrations, the best ratios of **5a**/**6**[10] were obtained by running reactions in CH_2Cl_2. The striking negative result obtained upon addition of molecular sieves (Table 1, entry 10) suggested the possible beneficial effect of water. Indeed, the deliberate addition of 20 equivalents of H_2O provided the best results (entries 12 and 13). Although the concurrent addition of the electrophilic Tf_2O and water appeared paradoxical at this time, it is important to note that their replacement by TfOH as lactonisation promoter (entry 14) led to markedly inferior results, as well as the joint use of various amounts of TfOH and Tf_2O[11] (not shown; see discussion below).

Table 1. Optimisation of conditions for the lactonisation of **4a**.



4d **5d** **6**

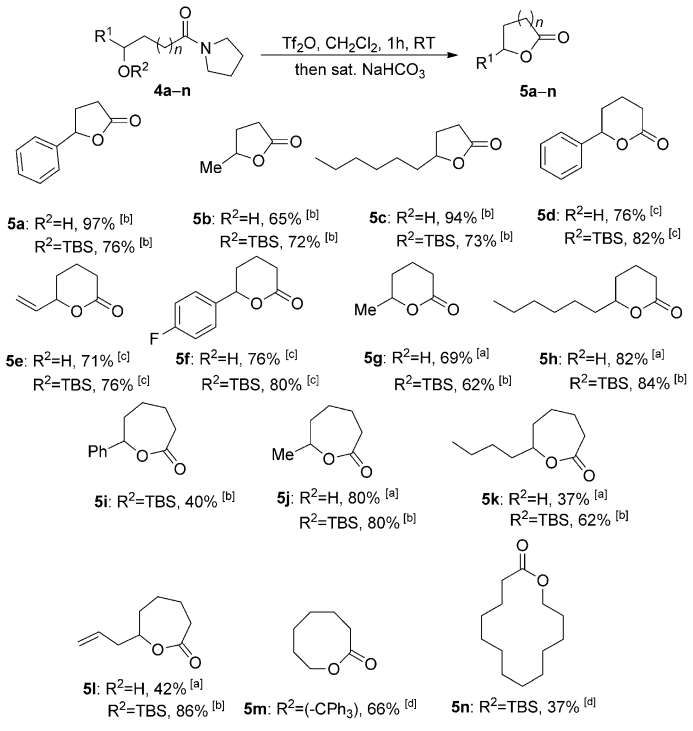
Entry	Solvent	Tf_2O [equiv]	H_2O [equiv]	**5d**/**6**[a]
1	CH_2Cl_2	1.05	–	67:33
2	CH_2Cl_2	2.00	–	75:25
3	CH_2Cl_2	3.00	–	64:36
4	$CHCl_3$	1.05	–	74:26
5	pentane	1.05	–	trace
6	benzene	1.05	–	50:50[b]
7	benzene	2.00	–	34:66
8	toluene	1.05	–	31:69
9	toluene	2.00	–	34:66
10[c]	CH_2Cl_2	1.05	–	SM
11	CH_2Cl_2	2.00	5	75:25
12	CH_2Cl_2	2.00	20	90:10
13[d]	CH_2Cl_2	2.00	20	86:14
14[e]	CH_2Cl_2	1.00	–	38:62

[a] Ratio determined by ^1H NMR spectroscopy. [b] ≈50% unreacted starting material was detected. [c] With molecular sieves (4 Å). [d] Run at 0.01 M concentration. [e] TfOH was used instead of Tf_2O. All reactions were worked up with saturated aqueous $NaHCO_3$; see the Supporting Information for details. SM = starting material.

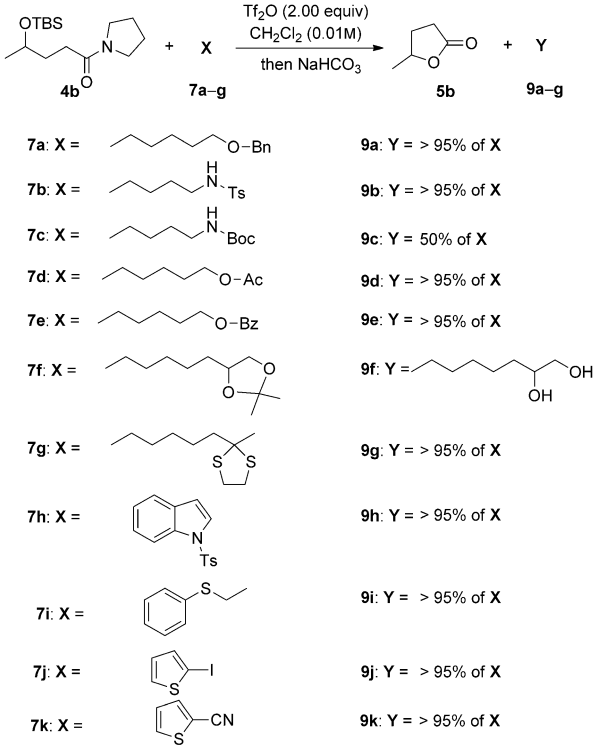
With optimised conditions in hand, we then inspected the scope of this protocol. As shown in Scheme 3, a broad range of substrates were tested. For the sake of comparison, the analogous substrates bearing a naked hydroxyl group were also subjected to the reaction, and the results are presented in combined fashion.

As depicted, various lactones of different ring sizes could be prepared by this direct cyclisation, bearing alkyl, alkenyl and aryl substituents. The use of a free hydroxyl-bearing substrate tends to be similarly effective to the use of a TBS-protected moiety, but as the lactone ring size increases this trend fades and the silyl ethers prove to be superior. Encouraging results were also obtained from the application of this methodology to the preparation of more challenging ring sizes (compounds **5m** and **5n**, Scheme 3), with the trityl protecting group proving to be an interesting alternative to TBS in one instance. All the lactonisations depicted in Scheme 3 proceed at room temperature and are generally complete within minutes (up to 1 h).

To ascertain whether this protocol would be of synthetic utility, it was of particular importance to test the tolerance of typical functional groups encountered in multistep synthetic sequences. To probe this, we added equimolar amounts of substrates decorated with such functional groups to reaction mixtures in which the lactonisation of protected hydroxyamide **4b** would take place and assessed their recov-



Scheme 3. Reaction conditions: [a] Tf_2O (1.05 equiv), [b] Tf_2O (2.00 equiv), [c] Tf_2O (2.00 equiv), H_2O (20.0 equiv), [d] Tf_2O (1.05 equiv), H_2O (20.0 equiv); see the Supporting Information for details.

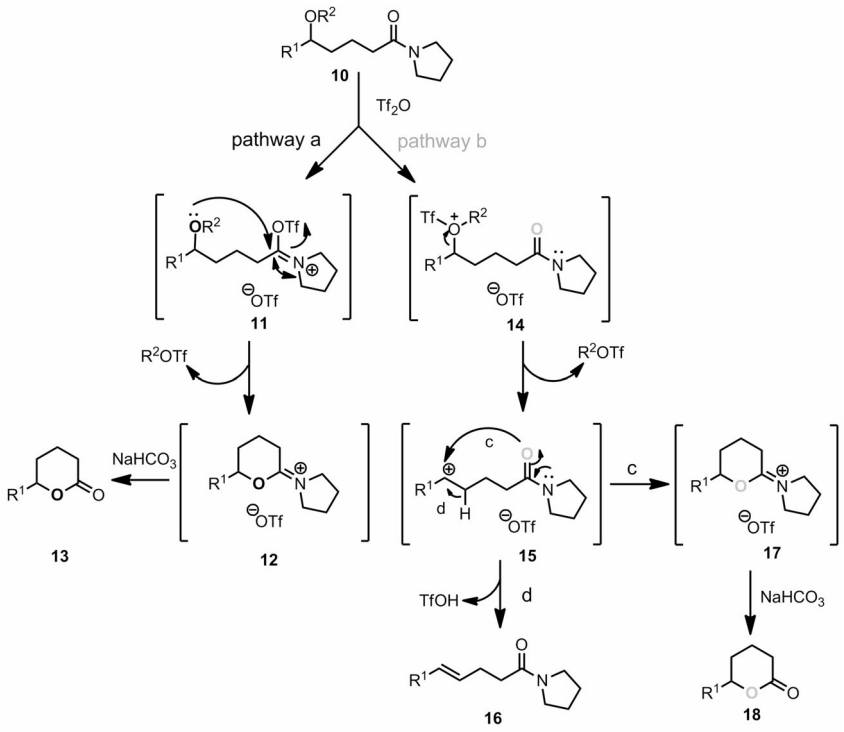


Scheme 4. Tolerance of typical functional groups to the reaction conditions.

ery at the end of the reaction. The results are depicted in Scheme 4.

As can be seen, the mild conditions and short reaction times under which the lactonisation operates allow the survival of most typical functional groups. These include sulfonamides, benzyl ethers and thioketals. The chemoselectivity of carbonyl activation by Tf_2O is reflected by the fact that most esters (acetate, benzoate) are oblivious to this reagent and are thus tolerated by the procedure. The limits of the method are encountered with acetonides and *tert*-butoxycarbonyl (Boc)-protected amines, which undergo deprotection under these conditions. Importantly, sulfides and various electron-rich aromatic heterocycles, such as indole or thiophene derivatives, are perfectly tolerated by the reaction conditions.

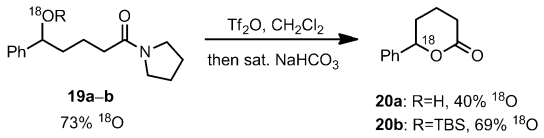
Our mechanistic hypothesis for the direct lactonisation is summarised in Scheme 5. We presume that triflic anhydride activates the amide to form the iminium triflate **11**, which is prone to nucleophilic attack by the pendant oxygen (path-



Scheme 5. Working mechanistic hypothesis.

way a). After ejection of triflate, the iminium ether intermediate **12** is hydrolysed during the post-reaction treatment with saturated aqueous $NaHCO_3$. Alternatively, the electrophilic triflic anhydride can react first with the alcohol/ether moiety to transiently generate a triflate/triflyloxonium leaving group (pathway b). Elimination of the last (presumably by E_1 pathways) or its direct intramolecular displacement by the amide carbonyl oxygen leads to either the olefin by-product **16** or an analogous iminium ether intermediate **17**.[12,13]

An experimentally appealing way to distinguish between pathways a and b would be to label one of the oxygen atoms. Thus, we prepared TBS-protected precursor **19b** in which the silylether oxygen was isotopically labeled as ^{18}O and subjected it to the reaction conditions.[11] In the event (Scheme 6), a near complete retention of the ^{18}O label was



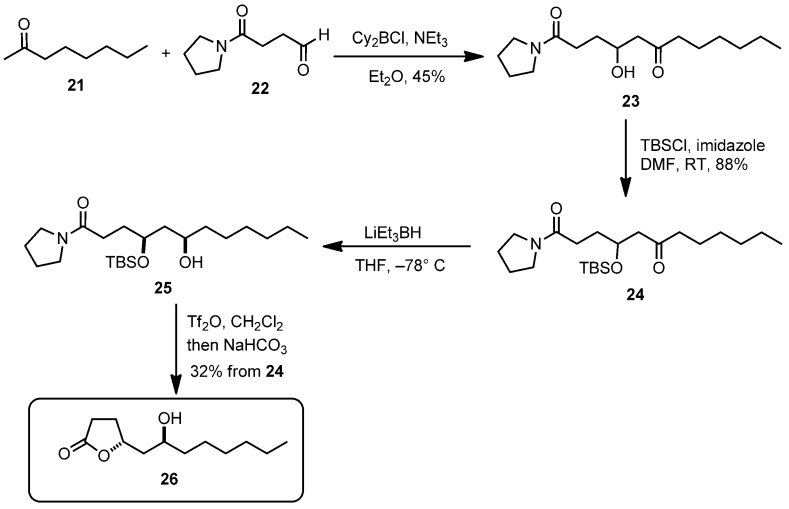
Scheme 6. ^{18}O-labelling experiments. Reaction conditions: Tf_2O (2.00 equiv), CH_2Cl_2, 10 min. Similar results were obtained upon addition of H_2O (20.0 equiv); see the Supporting Information for details.

observed (within experimental error). This result supports pathway a being operative in the case of TBS-protected ethers. Intriguingly, when the same experiment was performed on the free ^{18}O-labeled alcohol **19a**, significant erosion of the ^{18}O label was observed, suggesting that pathway b becomes competitive when the free alcohols are employed as substrates.

This mechanistic proposal further highlights the release of an equivalent of TBSOTf during the reaction of silylethers (and TfOH in the case of free alcohol substrates). In control experiments, we established that TBSOTf is also capable of promoting lactonisation under these reaction conditions, but with concomitant formation of significant amounts of elimination and other by-products.[11] Further experiments also suggest that the hydrolysis of TBSOTf into ultimately TBSOTBS (which can be detected by GC-MS analysis of reaction mixtures) proceeds very readily. Since, in our procedure, water is added to the reaction mixture after Tf_2O and as the conversion of the amide starting material into its iminium triflate **11** takes place virtually instantaneously (as determined by NMR experiments), it appears that the beneficial effect of water on these lactonisations could be due to its selective "mopping" of undesired TBSOTf as it is formed, thus protecting the most effective reaction pathway.

Finally, we applied this lactonisation method as the key step in the synthesis of *epi*-6-hydroxyundecan-4-olide **26**, one of the metabolites produced by the giant white butterfly *Idea leucona*.[14] As shown in Scheme 7, our short sequence begins with the aldol merger of the amide aldehyde **22** (available by Dess–Martin oxidation of the corresponding alcohol) with the boron enolate of commercially available 2-heptanone.[15] Following TBS-protection of the aldol product and *syn*-diastereoselective reduction employing Super-Hydride,[16] direct lactonisation affords the target compound in moderate overall yield. This streamlined, unoptimised synthetic route outlines what could be termed as an "amide strategy" for synthesis: it showcases the advantages of carrying a robust, amide-masked carboxyl through strongly basic conditions in steps such as an aldol addition or a carbonyl reduction (which might not have been tolerated by the carboxylic acid or ester[17] analogues of **22** and **25**), while allowing for its selective activation at a late stage of the synthetic pathway.[18]

Herein, we disclose a new approach to the synthesis of lactones by room-temperature cyclisation of alcohols and ethers onto amides. This allows a direct disconnection of lactone products back to fully protected starting materials, but without requiring any wasteful deprotection steps.[19] The notion that the amide functional group can be taken through demanding synthetic sequences as a robust carboxylate mask and at the same time be selectively activated under mild conditions at room temperature is intriguing.[18] The elaboration of this concept is currently underway in our laboratories.



Scheme 7. Four-step synthesis of *rac-epi*-6-hydroxyundecan-4-olide (**26**).

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Keywords: amides · electrophilic activation · lactones · mechanistic studies · triflic anhydrides

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[9] Additional protecting groups screened, including (but not limited to) Bn, MOM, SEM and THP, all proved inferior to TBS; see the Supporting Information for details.

[10] No efforts were made to fully characterise compound **6** beyond NMR spectroscopy; see the Supporting Information for details.

[11] See the Supporting Information for details.

[12] The intermediacy of **12** and **17** prior to hydrolysis has been confirmed by online NMR analysis of reaction mixtures; see the Supporting Information for details.

[13] Importantly, the isolated olefin by-product **16** ($R^1 = Ph$) does not undergo conversion to **12** or **17** under either the reaction conditions or upon addition of TfOH.

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[18] For a similar synthetic concept applied to the use of alkynes ("alkyne strategy"), see: a) B. M. Trost, A. H. Weiss, *Angew. Chem.* **2007**, *119*, 7808; *Angew. Chem. Int. Ed.* **2007**, *46*, 7664; b) B. M. Trost, J. D. Sieber, W. Qian, R. Dhawan, Z. T. Ball, *Angew. Chem.* **2009**, *121*, 5586; B. M. Trost, J. D. Sieber, W. Qian, R. Dhawan, Z. T. Ball, *Angew. Chem. Int. Ed.* **2009**, *48*, 5478.

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