Cascade Rearrangement of Furylcarbinols with Hydroxylamines: Practical Access to Densely Functionalized Cyclopentane Derivatives

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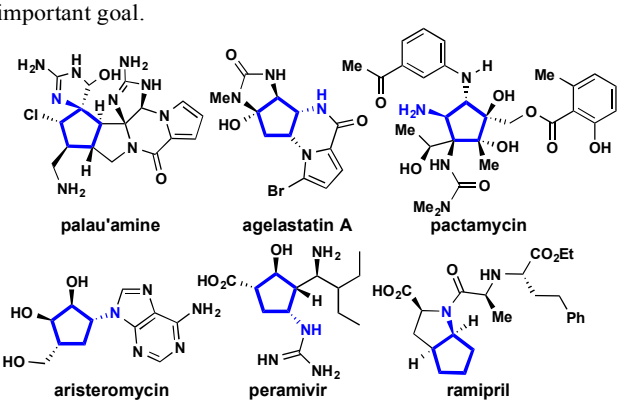
This article describes the aza-Piancatelli rearrangement with hydroxylamines to 4-aminocyclopentenones and subsequent transformations that highlight the versatility of the cyclopentene scaffold and the value of the hydroxylamine nucleophile in this transformation.

Introduction

The cyclopentane ring system is prevalent in major natural product families, as well as in a wealth of biologically active molecules.[1] In many well-known cases, such as palau'amine,[2] agelastatin A,[3] pactamycin[4] and aristeromycin,[5] a densely functionalized cyclopentane core bearing nitrogen substituents is the defining structural feature of these important molecules (Scheme 1).[1b] This structural motif is also well represented in synthetic molecules, such as peramivir, ramipril, Janssen CCR2 antagonist and Merck carbanucleoside HCV inhibitor.[1b] Of these, ramipril is one of the top performing generic drugs in the last decade that has been recommended for the treatment of high blood pressure and heart failure.[6] Consequently, the development of new synthetic methodologies to access densely functionalized aminocyclopentanes with improved efficiency, step economy and accessibility of novel chemotypes, remains an important goal for organic chemists.

Approaches for the synthesis of functionalized aminocyclopentanes rely primarily on the nitroso Diels–Alder cycloaddition,[7] the intramolecular Henry reaction[8] and methodology such as RCM,[9] [3+2] cycloaddition[10] and the cascade rearrangement of furan derivatives.[11] A highly attractive direct route to densely functionalized aminocyclopentanes is through the cascade rearrangement of furylcarbinols, referred to as the aza-Piancatelli reaction.[12] This approach takes advantage of furfural, a commodity chemical derived from agricultural byproducts, as the renewable and inexpensive starting material. Recent progress in the aza-Piancatelli rearrangement with aniline nucleophiles has enabled the direct synthesis of *trans*-substituted 4-amino-cyclopentenones[13] and aza-spirocycles in high yield,[14] as well as the 5-step synthesis of a hNK1 inhibitor.[13a] Although an efficient and practical method, the aza-Piancatelli rearrangement is limited to the use of aromatic amines as the nucleophile, severely restricting its utility. Due to the synthetic importance, a general method for the synthesis of aminocyclopentanes with non-aromatic amines through the cascade rearrangement of furylcarbinols remains an unmet, but important goal.



Scheme 1. Cyclopentylamines in natural and synthetic products.

Herein we report the efficient synthesis of hydroxylamine-substituted 4-aminocyclopentenones whose synthetic utility is highlighted through further elaboration of the core structural unit. The fact that hydroxylamines are used makes this approach general and flexible, as cleavage of the N–O bond

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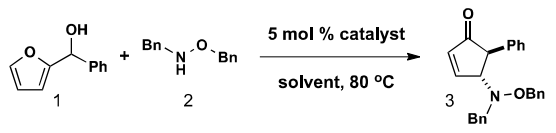
[d] *† Electronic supplementary information (ESI) available: Experimental details,spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra. CCDC 986010. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x/*

reveals a primary or secondary amine that can be subsequently manipulated. A detailed mechanistic investigation into this transformation is the subject of a separate paper.[15]

Results and Discussion

Guided by our mechanistic investigations we focused on amines that possess similar properties, such as pKa, to anilines.[13e] With this in mind, we began our investigations by testing the viability of commercially available *N*-benzylhydroxylamine and *O*-benzylhydroxylamine as nucleophiles. Unfortunately, these substrates would not participate in the rearrangement, and only starting material was recovered from these reactions. Speculating that the free amine or hydroxyl group may bind too strongly to our catalyst of choice, we decided to evaluate *N*-substituted *O*-protected hydroxylamines. To our delight, readily accessible *N*-benzyl-*O*-benzyl hydroxylamine participated in the rearrangement to give the desired *trans*-4,5-disubstituted aminocyclopentenone **3** in excellent yield using our previously optimized reaction conditions (5 mol % $Dy(OTf)_3$ in reagent grade MeCN at 80 °C) (Table 1, entry 1). However, a small solvent screen identified nitromethane ($MeNO_2$) as a superior solvent due to greatly reduced reaction times (30 min vs 18 h, entry 2, see ESI†). Dysprosium(III) triflate was chosen as the catalyst because of our long-term interest in exploring the chemistry of this Lewis acid.[13a,13e,14,17] However, to demonstrate the flexibility of this aza-Piancatelli rearrangement it was instructive to explore the use of other rare-earth Lewis acids, as well as Brønsted acids. Importantly, this rearrangement is tolerant of a number of catalysts and it can be envisioned that $Dy(OTf)_3$ can be replaced with other rare-earth Lewis acids or Brønsted acids if necessary.

Table 1. Optimization of the rearrangement conditions.



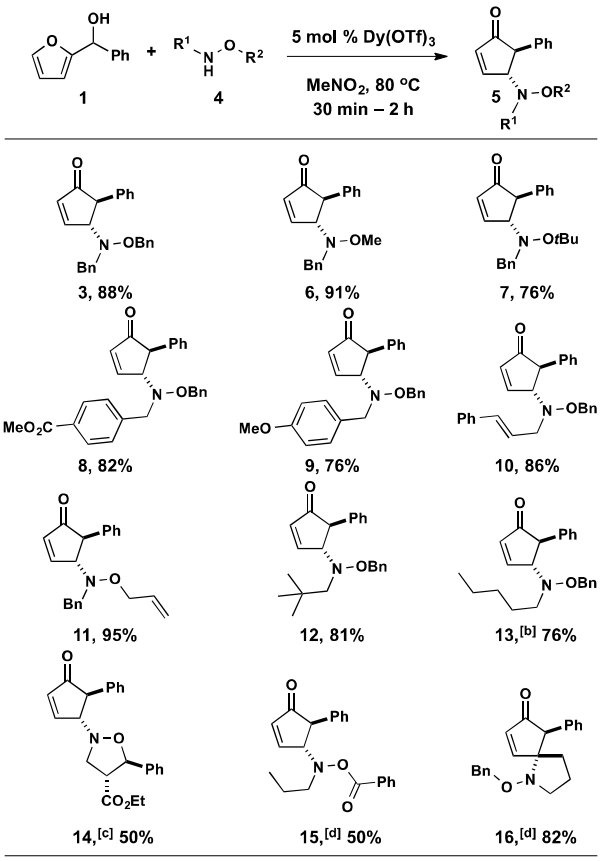
entry	solvent	catalyst	time	yield (%)[a]
1	MeCN	$Dy(OTf)_3$	18 h	87
2	$MeNO_2$	$Dy(OTf)_3$	30 min	88
3	$MeNO_2$	$Sc(OTf)_3$	20 min	76
4	$MeNO_2$	$La(OTf)_3$	40 min	91
5	$MeNO_2$	$Gd(OTf)_3$	30 min	88
6	$MeNO_2$	$Yb(OTf)_3$	40 min	94
7	$MeNO_2$	$DyCl_3$	10 h	54
8[b]	$MeNO_2$	PMA	5 min	decomp
9[c]	$MeNO_2$	TsOH	15 min	35
10[c]	$MeNO_2$	Amberlyst® 15	6 h	35

[a] Isolated yields. [b] PMA = phosphomolybdic acid. [c] 100 mol % of catalyst was used.

To explore the general nature of the transformation with hydroxylamines, a number of *O*-substituted hydroxylamines were prepared. These hydroxylamines can be easily synthesized in two steps from the hydroxylamine hydrochloric acid salt via reductive amination.[16] We found that a variety of alkyl substituents at both *N* and *O* were well tolerated. The best results were achieved with 5–10 mol % $Dy(OTf)_3$ in $MeNO_2$ at 80 °C and it is important to note that no special precaution was taken to remove water or air. The results of the transformation with phenyl furylcarbinol **1** are summarized in Table 2. Varying the substituent from benzyl to methyl or even a bulky *t*-butyl group at the *O*-terminus of *N*-benzyl-hydroxylamine afforded the desired cyclopentenones in high yield (**3**, **6** and **7**). Modifying the electronic nature of the benzyl group on nitrogen to an electron withdrawing *p*-CO_2Me (**8**) or electron donating *p*-OMe (**9**) had little effect on the yield, and only a small effect on rate (2 h vs 1 h). Cinnamaldehyde derivative **10** and allylic alcohol derivative **11** are readily obtained in high yield. Changing the group on nitrogen from benzylic to neopentyl (**12**) worked well, but the linear *n*-pentyl substituent (**13**) required an increased catalyst loading (10 mol % $Dy(OTf)_3$) for the reaction to proceed at a reasonable rate. We were pleased to discover that a cyclic hydroxylamine and *O*-benzoyl hydroxylamine also participate in the reaction to give **14** and **15** in moderate yield. Finally, an example of an intramolecular hydroxylamine-aza-Piancatelli rearrangement demonstrates the universal applicability of the hydroxylamine nucleophiles to this rearrangement and gives spirocyclic cyclopentenone **16** in good yield as a single diastereomer.

Following our investigation of suitable hydroxylamines, we explored a range of furylcarbinols. The results of this evaluation are summarized in Table 3. Adding an electron-donating or electron-withdrawing substituent to the phenyl ring of the furylcarbinol had no effect on the efficiency of the reaction but, in accord with the aniline aza-Piancatelli rearrangement, an increased reaction rate was observed with the electron-donating *p*-OMe group (**19** vs. **20**).[13a,13e] The rearrangement also worked well with the heterocyclic thiophene furylcarbinol providing **21** in 92% yield. Sterically bulky triisopropylphenyl furylcarbinol readily rearranged to give **22** in 80% yield. The bis-phenyl substituted tertiary furylcarbinol underwent the rearrangement, giving **23** and **24** bearing a quaternary carbon alpha to the carbonyl.[17] Finally, alkyl-substituted furylcarbinols rearranged, but in a similar manner to utilizing non-bulky substituents on the nitrogen (**13**, Table 2), an increased catalyst loading was required for these transformations, and yields were diminished to around 50% regardless of the nucleophile used (Table 3, entries **25 – 27**). It is worth noting that the activation of the alkyl-substituted furylcarbinols is more challenging, evident by longer reaction times required for completion compared to the corresponding furylcarbinols bearing an aryl group. For example, a 48 h reaction was required for the synthesis of **25** using 10 mol % $Dy(OTf)_3$, but only 30 minutes were required for the synthesis of **20** using 5 mol % $Dy(OTf)_3$. It is plausible that the extended reaction time leads to decomposition of one, or all, reactive components.

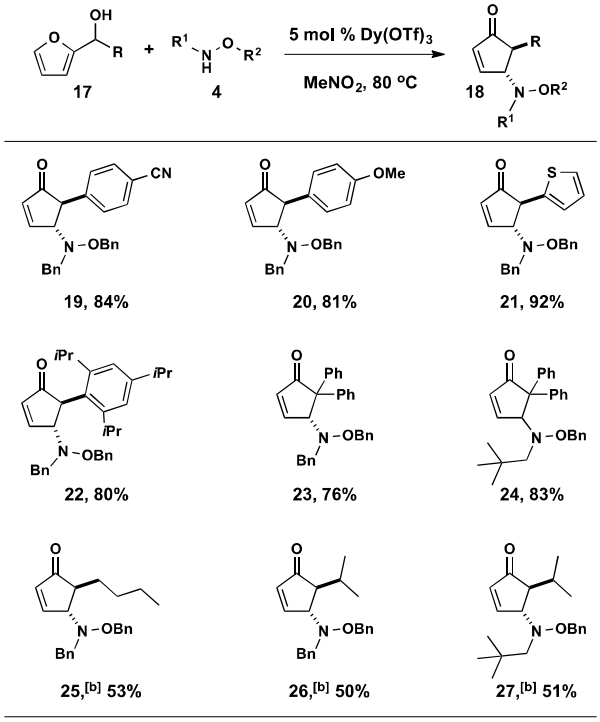
Table 2. Scope of the rearrangement with substituted hydroxylamines.[a]



[a] Isolated yields. [b] Reaction performed with 10 mol % $Dy(OTf)_3$. [c] Isolated as a 1:1 mixture of *trans* diastereomers. [d] Reaction performed with 30 mol % $Dy(OTf)_3$ at rt (58 h).

With a variety of hydroxylamine-substituted cyclopentenones in hand, we sought to elaborate this basic framework. Straightforward modification of the ketone via a modified Luche reduction delivered the allylic alcohol in up to 20:1 diastereomeric ratio (d.r.), while 1,2-addition of a Grignard reagent could be achieved using Knochel's conditions (**30** and **28**, respectively).[18] Low diastereoselectivity was observed when other conditions for the 1,2-reductions or Grignard addition reaction were employed. Once formed, allylic transposition of the tertiary alcohol using pyridinium chlorochromate (PCC) afforded α-amino cyclopentenone **29** in a transformation that effectively switches the positions of the amine and R-group relative to the ketone.[19] Importantly, the *trans*-stereochemistry established during the 4π electrocyclization of the aza-Piancatelli rearrangement is retained during this transposition. Direct cleavage of the N–O bond of **23** and **24** using Pd/C hydrogenation conditions cleanly gave the corresponding primary and secondary amine **31** and **32** in quantitative yield (Scheme 2).

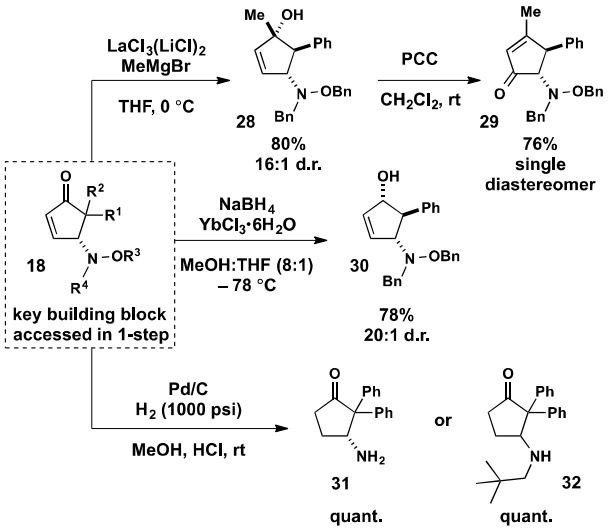
Table 3. Scope of furylcarbinols in the hydroxylamine aza-Piancatelli rearrangement.[a]



[a] Isolated yields. Reaction times vary from 30 min to 96 h, see ESI† for details. [b] Reaction performed with 10 mol % $Dy(OTf)_3$.

Encouraged by the successful cleavage of the N–O bond under hydrogenation conditions and the ample precedent for cleaving the relatively weak N–O bond in the literature, we sought to exploit this intrinsic feature to unveil the primary or secondary amine group. To our surprise, cleaving the N–O bond of *trans*-4,5-disubstituted aminocyclopentenone (**18**) with traditional methods (H_2, Pd/C;[20] SmI_2;[16a] $Mo(CO)_6$;[21] Zn/HCl,[22] etc.) was unsuccessful, resulting in recovered starting materials or more often decomposition. Given the success of cleaving the N–O bond in cyclopentenone **23** and **24** bearing a fully substituted carbon stereocenter at the 5-position of the cyclopentenone, we hypothesized that the presence of the hydrogen alpha to the carbonyl makes 4-aminocyclopentenone compounds more susceptible to decomposition.

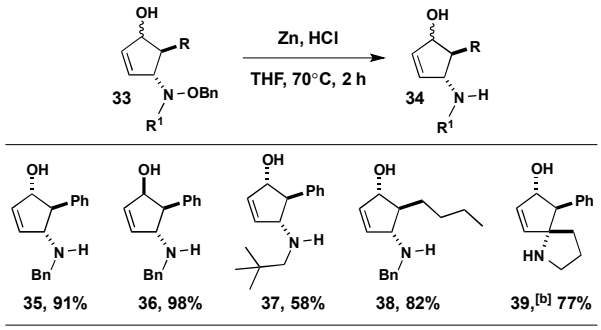
Although disappointing that the N–O bond could not be cleaved directly, the challenges with manipulating the substituted 4-aminocyclopentenone adducts parallels what has been observed while attempting to elaborate related cyclopentenone cores.[23] To eliminate problems associated with the sensitivity of the cyclopentenone adduct, transformations are often conducted from the corresponding allylic alcohol. For example, Batey and co-workers successfully utilized this approach while elaborating a 4,5-diaminocyclopentenone product en route to (±)-agelastatin A.[3c] To examine this alternative strategy and investigate its generality with our system, several cyclopentenone products were reduced to the corresponding allylic alcohol. We were delighted to find that Zn/HCl conditions enabled the N–O bond cleavage on a variety



Scheme 2. Selected functionalization of the cyclopentenone scaffold. The relative stereochemistry of **28** was assigned by analogy to **30**.

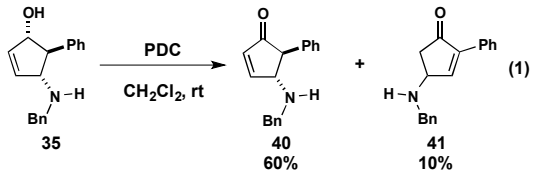
of allylic alcohols, as summarized in Table 4. The results from these studies show that the nature of the substituents on the cyclopentenol or the substituent on the nitrogen or oxygen do not affect the success of the N–O bond cleavage. Of note, the N–O bond cleavage of either the 1,2-*cis* or 1,2-*trans*-hydroxy intermediates provides rapid access to either the 1,2-*cis*-2,3-*trans*-cyclopentene or the 1,2-*trans*-2,3-*trans*-cyclopentene scaffold possessing three contiguous stereocenters in up to 98% yield, **35**–**38**.[24] Importantly, this approach was also compatible with the aza-spirocycle motif **39**, which is often more sensitive toward decomposition.

Table 4. Scope of the *N–O* bond cleavage from the allylic alcohol.[a]



[a] Isolated yields. [b] From an 8:1 mixture of diastereomers.

Lastly, the synthesis of the elusive 4-aminocyclopentenone can be achieved using an oxidation strategy that proceeds through the allylic alcohol (Eq. 1). After a survey of different oxidants, a PDC oxidation proved optimal and the desired 4-aminocyclopentenone **40** was isolated in 60% yield, along with 10% of the more thermodynamically favored cyclopentenone **41**.[12] It is worth noting that the rearranged product (**41**) is not observed by ^{1}H NMR of the crude reaction mixture and it is only upon column chromatography or extended storage that **41** is observed. Although well known in the Piancatelli rearrangement with water and exploited for prostaglandin alkaloid synthesis,[25] this is the first time we have observed this behavior with aminocyclopentenones.



Conclusions

In summary, we have developed a new method to access cyclopentenones bearing hydroxylamine substituents. This powerful transformation aids in satisfying the need to access this important scaffold using more versatile amine nucleophiles. Densely functionalized *trans*-substituted 4-aminocyclopentenones can be synthesized in a single step from simple furylcarbinols. Furthermore, we explored the elaboration of this basic framework utilizing intrinsic points of functionalization. The lessons and insights gained while elaborating the 4-aminocyclopentenone scaffold will help lay the necessary groundwork for future applications of this rearrangement in the synthesis of biologically active compounds.

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