Rearrangement Reactions

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Versatile Method for the Synthesis of 4-Aminocyclopentenones: Dysprosium(III) Triflate Catalyzed Aza-Piancatelli Rearrangement**

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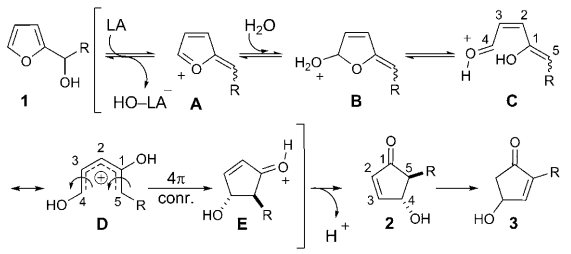
In memory of Marianna Rovis

Well-represented in natural products and biologically active molecules, the cyclopentenone scaffold has long been an inspiration for the development of new methodologies.[1] In 1976, Piancatelli and co-workers reported a new method for the synthesis of 4-hydroxycyclopentenone derivatives by an acid-catalyzed rearrangement of suitable 2-furylcarbinols (Scheme 1).[2] The overall transformation is believed to proceed through a cascade sequence that terminates with a 4π electrocyclic ring closure of a pentadienyl cation (**D**), analogous to the Nazarov cyclization.[3]



Scheme 1. Proposed mechanism of the Piancatelli reaction. LA = Lewis acid, conr. = conrotatory

Investigations by Piancatelli and co-workers focused exclusively on accessing 4-hydroxycyclopentenones, presumably because reaction development was largely driven by application of this methodology to the synthesis of prostaglandins.[4] The synthetic utility of the Piancatelli rearrangement has been limited because the reaction often requires stoichiometric amounts of acid, dilute reaction conditions (<0.005 M), and excess water. Furthermore, there has been only one subsequent investigation that probes this interesting cascade rearrangement to access compounds besides substituted 4-hydroxycyclopentenones. This seminal study by Denisov and et al. also required stoichiometric amounts of acid (BF_3·OEt_2 or *p*-TsOH) and was limited to 2-furylcarbinols that were activated with a cobalt/alkyne complex.[5]

The Piancatelli rearrangement caught our attention because both the cascade rearrangement and access to *trans*-4,5-disubstituted cyclopentenones appear ideally suited for various applications in synthesis. We reasoned that an efficient catalytic aza-Piancatelli rearrangement would be a powerful synthetic reaction for the preparation of *trans*-substituted 4-amino-5-alkylcyclopentenones, a functional scaffold that is rich in potential for the synthesis of biological and medicinal compounds. Few processes are available for the synthesis of 4-aminocyclopentenones,[6] and all of the previously reported methods require multiple steps and typically lack substitution at the 5-position. Herein, we report a mild catalytic single-step procedure for the conversion of readily available 2-furylcarbinols into their corresponding *trans*-substituted 4-amino-5-alkylcyclopentenones.

Our investigation began by identifying a catalyst capable of activating 2-furylcarbinols in the presence of potentially problematic Lewis basic amines. We were encouraged by a report by Li and Batey that rare-earth Lewis acids mediate the rearrangement of furfural-derived iminium cations in the presence of excess Lewis basic amines.[7] Therefore, we hypothesized that such acids would allow us to extend the range of possible nucleophiles beyond electron-deficient *para*-substituted anilines.[8]

Initial studies were conducted by examining the addition of commercially available *para*-iodoaniline **5** to furylcarbinol **4** in the presence of 5 mol % of either scandium or dysprosium trifluoromethanesulfonate (Table 1). We were pleased to find that both Lewis acids catalyzed the desired transformation, affording 4-aminocyclopentenone **6** in excellent yield as a single diastereomer (Table 1, entries 1 and 2). The rearrangement was found to be most effective at 80 °C (Table 1, entry 3). Although 5 mol % of triflic acid can serve as an active catalyst for this rearrangement (Table 1, entry 4), control experiments demonstrated that a trace quantity of triflic acid was not solely responsible for the catalysis when a metal triflate was employed (Table 1, entries 5 and 6).[9] We chose to develop the reaction with $Dy(OTf)_3$ because of its lower cost compared to $Sc(OTf)_3$ and because it is experimentally easier to handle than triflic acid.[10] Lewis acid reactions mediated by $Dy(OTf)_3$ have not attracted tremendous interest from the synthetic community, despite the fact that it exhibits similar reactivity and shares the advantageous properties of other lanthanide salts: low toxicity and cost, ease of handling, and stability toward moisture.[11]

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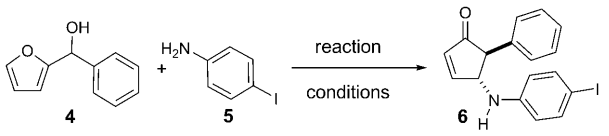
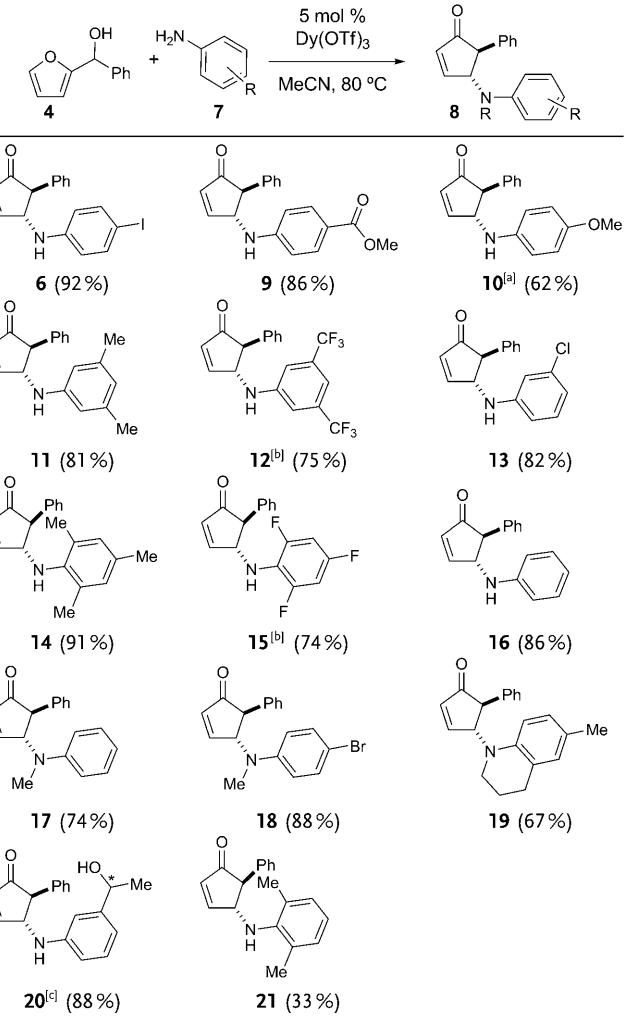
Table 1: Optimization of the rearrangement conditions.



4 5 6

Entry[a]	Catalyst (mol%)	*T* [°C]	*t* [h]	Yield [%]
1	$Sc(OTf)_3$ (5)	40	3	83
2	$Dy(OTf)_3$ (5)	40	2	79
3	$Dy(OTf)_3$ (5)	80	0.5	92
4	HOTf (5)	80	0.5	62
5[b]	HOTf (5) K_2CO_3 (100)	80	4	0
6	$Dy(OTf)_3$ (5) K_2CO_3 (100)	80	1	93

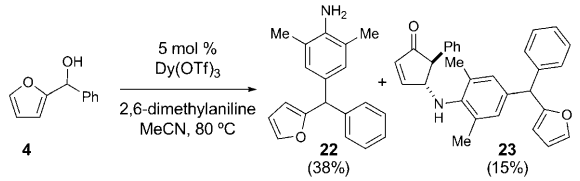
[a] Reaction conducted in MeCN. [b] The starting material was recovered from the reaction.



Scheme 2. Scope of the rearrangement with substituted anilines. [a] 20 mol% $Dy(OTf)_3$. [b] 3 equiv of the corresponding aniline. [c] Formed as a 1:1 ratio of diastereomers at the stereocenter marked with an *. Yields reported are those of the isolated products.

Under the optimized reaction conditions (5 mol% $Dy(OTf)_3$, MeCN, 80°C), we investigated the scope of this transformation. Scheme 2 summarizes results obtained with *ortho*-, *meta*-, and *para*-substituted aniline derivatives. The reaction of anilines substituted at the *para*- or *meta*-positions generated the best results. Sterically hindered 2,4,6-trimethylaniline also successfully participated in the reaction (**14**). Secondary acyclic and cyclic anilines produced the desired product in 74%, 88%, and 67% yield, respectively (**17**, **18**, and **19**).

Several additional observations merit note. Typically, it is difficult to prevent product isomerization (Scheme 1, **2**→**3**) in the Piancatelli rearrangement; however, presumably because of the mild nature of the $Dy(OTf)_3$ catalyst, product isomerization was not observed in the aza-Piancatelli rearrangement. One significant side-reaction did occur when 2,6-dimethylaniline was employed. In this case, **21** was formed in only 33% yield (Scheme 2), with the rest of the remaining starting material consumed by Friedel–Crafts alkylation to give **22** and **23** (Scheme 3).[12]



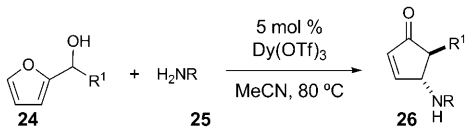
Scheme 3. Products resulting from Friedel–Crafts alkylation.

Subsequently, we performed a series of experiments to explore the initial scope of the furylcarbinol component **24** using **25** in this rearrangement to give **26**. As shown in Table 2, the rearrangement is compatible with 2-aryl furylcarbinols possessing electron-donating or electron-withdrawing groups on the aromatic ring (Table 2, entries 1–6). It is noteworthy that 2-alkyl-substituted furylcarbinols can be accommodated without a significant loss in reactivity (Table 2, entries 7–12). Increasing the steric bulk of the alkyl group on the 2-substituted furylcarbinol from methyl to isopropyl groups appreciably decreased the formation of the competing Friedel–Crafts alkylation with *meta*-chloroaniline (Table 2, entries 8 and 11).

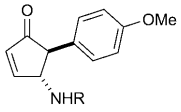
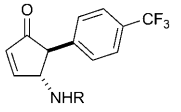
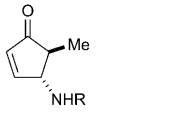
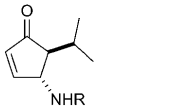
We believe that the high *trans* diastereoselectivity is a result of a 4π conrotatory electrocyclization.[13] It seems likely that the initial step in the cascade rearrangement involves loss of the alcohol and the formation of a stabilized carbocation. At this point, the stabilized carbocation can react with the aniline through two predominant pathways: Friedel–Crafts alkylation at the benzylic position or addition at the 5-position of the furylcarbinol, the latter triggering the product-forming cascade reaction.

To highlight the synthetic utility of this methodology, we began to explore the application of the cascade rearrangement for the efficient synthesis of biological and medicinal molecules. A recent structure–activity relationship (SAR) study by Merck found 1,2-*trans*-2,3-*trans*-cyclopentane-based scaffolds of type **39** to be comparable to the current clinical

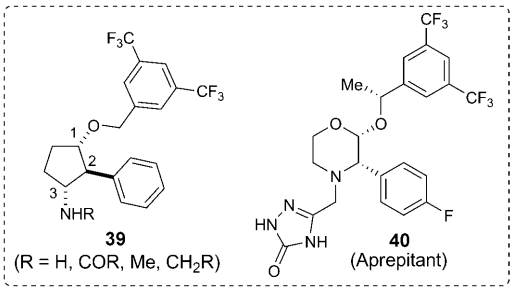
Table 2: Scope of the rearrangement with various 2-furylcarbinols.



24 **25** **26**

Entry	Product	R	Yield [%]
1[a]		*p*-IC_6H_4 (**27**)	68
2[a]		*m*-ClC_6H_4 (**28**)	82
3[a]		2,4,6-$Me_3C_6H_2$ (**29**)	89
4		*p*-IC_6H_4 (**30**)	83
5		*m*-ClC_6H_4 (**31**)	87
6[b]		2,4,6-$Me_3C_6H_2$ (**32**)	78
7		*p*-IC_6H_4 (**33**)	68
8[c]		*m*-ClC_6H_4 (**34**)	10
9		2,4,6-$Me_3C_6H_2$ (**35**)	74
10		*p*-IC_6H_4 (**36**)	73
11		*m*-ClC_6H_4 (**37**)	52
12		2,4,6-$Me_3C_6H_2$ (**38**)	89

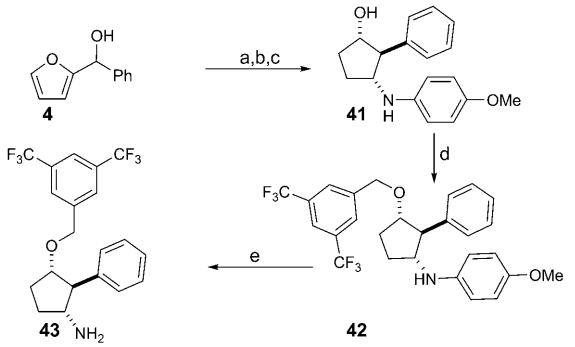
[a] Reaction conducted at RT. [b] 10 mol% $Dy(OTf)_3$. [c] Products arising from Friedel–Crafts alkylation were mainly observed. Yields reported are those of the isolated products.



Scheme 4. Representative cyclopentane-based hNK1 antagonist.

compound **40** in assays of hNK1 inhibition (Scheme 4).[14] Aprepitant (**40**) is an hNK1 antagonist and FDA approved for use as an antiemetic for chemotherapy-induced nausea and vomiting.

The synthesis of a cyclopentane scaffold containing an oxygen functionality at the C1 position, the required aryl group at the C2 position, and a functionalizable amine group at the C3 position began with the rearrangement of **4** with *para*-anisidine on a gram scale (Scheme 5). Luche reduction of cyclopentenone **10** gave the 1,2-*trans*-2,3-*trans*-cyclopentene-based scaffold in two steps from commercially available reagents. Subsequent alkene reduction and hydroxyl alkylation with 3,5-bis(trifluoromethyl)benzyl bromide and sodium hydride gave the racemic ether **42**. Oxidative dearylation of the *para*-methoxyphenyl group with periodic acid (H_5IO_6) provided the primary amine.[15] The hNK1 binding affinity for racemic cyclopentane **43** was moderate ($IC_{50} = 5.7$ nM); however, enhanced affinity ($IC_{50} < 0.1$ nM) and aqueous solubility were achieved by simple derivatization of **43**.[14]



Scheme 5. Direct synthesis of the cyclopentane scaffold: a) 5 mol% $Dy(OTf)_3$, *para*-anisidine, MeCN, 80 °C, 60% (1 gram scale) b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 98% (2:1 *trans/cis*); c) 10 mol% Pd/C, H_2, MeOH, 500 psi, 76% (2:1 *trans/cis*; **41** = 49%); d) NaH, 3,5-bis(trifluoromethyl)benzyl bromide, THF, 75%; e) H_5IO_6, H_2SO_4, MeCN/H_2O (1:1), RT, 58%. THF = tetrahydrofuran.

In conclusion, we have developed an efficient aza-Piancatelli rearrangement that constructs a carbon–carbon bond plus a carbon–nitrogen bond and two stereocenters in a single operation. This strategy offers a practical solution for the synthesis of 4-aminocyclopentenones, a versatile building block for the synthesis of structurally diverse biologically active molecules. Reactions are performed in reagent grade acetonitrile, open to air, with commercially available $Dy(OTf)_3$. Further investigation of this rearrangement and its application toward complex synthetic targets will be forthcoming.

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