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Calcium(II)-Catalyzed Aza-Piancatelli Reaction

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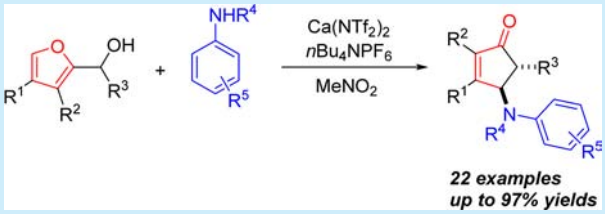
Supporting Information

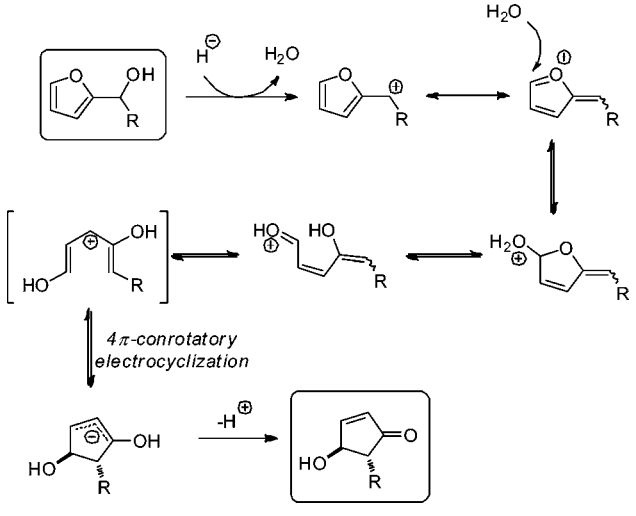
ABSTRACT: The first examples of calcium-catalyzed aza-Piancatelli reactions between substituted 2-furylcarbinols and aniline derivatives are described. A variety of 4-aminocyclopentenones have been synthesized stereoselectively in high yields. The experimental procedure utilizes simple salts and does not require specific precautions.



Because of their multifunctional properties, cyclopentenones are very useful intermediates for the synthesis of natural products of therapeutic value. The Pauson–Khand[1] and the Nazarov[2] reactions are some of the most commonly used methods to generate such building blocks. Whereas the Nazarov reaction and its variants have been extensively studied by several groups,[3] including ourselves,[4] a related intriguing transformation remained in its shadow for many years. In 1976, Piancatelli et al. described the synthesis of 4-hydroxycyclopentenones from 2-furylcarbinols and water in the presence of strong Brønsted acids (Scheme 1).[5] The common feature between the Nazarov and the Piancatelli reactions is that their stereoselectivity relies on the conrotatory 4π-electrocyclization of a pentadienyl carbocation intermediate.[6]

The Piancatelli reaction has gained a renewed interest in the past decade. This reaction can now be carried out by catalytic systems based on lanthanides (La, Dy) or group 13 elements (In).[7] Interestingly, several reports showed that the reaction is not limited to the use of water as nucleophile but is also compatible with amines, alcohols, or arenes. In the specific case of anilines, the Piancatelli reaction leads to 4-aminocyclopentenones.[7a] These compounds are highly desirable as they are potential intermediates to aminocyclopentitol frameworks, which are present in a variety of bioactive molecules such as peramivir,[8] pactamycin,[9] or trehazolin (Figure 1).[10]

Scheme 1. Mechanism of the Piancatelli Reaction



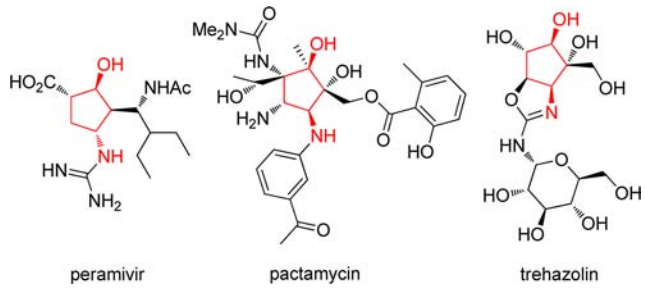


Figure 1. Natural products containing an aminocyclopentitol moiety.

In spite of the great synthetic interest of the aza-Piancatelli reaction, some important issues remain to be addressed to make this chemistry more appealing. First, an in-depth scope of the reaction is necessary to fully demonstrate its usefulness in organic synthesis. For instance, the influence of the substitution of the furan ring has yet to be examined. Second, there is a strong demand for a catalytic system that would be easier to implement than those used so far in terms of price, toxicity, and handling. In this context, group 1 and 2 metal salts look particularly attractive, especially those based on calcium.[11] Niggemann and others have demonstrated the high efficiency of simple calcium salts such as $Ca(NTf_2)_2$, which combined with a weakly coordinating anion source gives rise to exquisite

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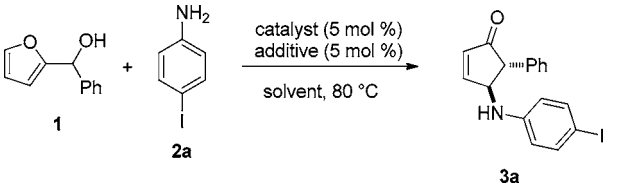
Lewis acids in catalysis.[12,13] In addition, such species are air- and moisture-stable and do not require the use of distilled solvents. The known lanthanide-like behavior of calcium complexes could be used to mimic the reactivity observed with lanthane- or dysprosium-based catalysts.[11a] Herein, we show that simple calcium derivatives are efficient catalysts for the aza-Piancatelli reaction. Polyfunctionalized 4-aminocyclopentenones have been obtained in a highly selective fashion, starting from various substituted furan derivatives.

We started our investigation using 2-furyl(phenyl)methanol **1**, *p*-iodoaniline **2a**, and group 1 and 2 metal triflimidates as catalysts (Table 1). In the case of $LiNTf_2$, the reaction required

Table 1. Screening of Group 1 and 2 Lewis Acids in the Catalytic Cyclization of 2-Furyl(phenyl)methanol 1 with *p*-Iodoaniline 2a[a]



1 **2a** **3a**

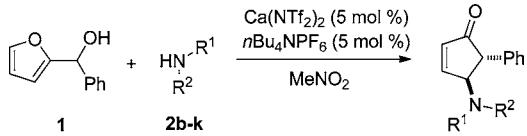
entry	catalyst	additive	solvent	time (min)	yield (%)
1	$LiNTf_2$		$MeNO_2$	120	82
2	$Mg(NTf_2)_2$		$MeNO_2$	45	81
3	$Ca(NTf_2)_2$		$MeNO_2$	45	90
4	$Ba(NTf_2)_2$		$MeNO_2$	80	84
5	$Ca(NTf_2)_2$		DCE	60	86
6	$Ca(NTf_2)_2$	*n*-Bu_4NPF_6	$MeNO_2$	10	92
7	$Ca(NTf_2)_2$	*n*-Bu_4NPF_6	DCE	60	91
8	$Ca(NTf_2)_2$	*n*-Bu_4NPF_6	$MeNO_2$	30	91[b]
9	$Ca(NTf_2)_2$	*n*-Bu_4NPF_6	$MeNO_2$	90	87[c]
10	$Mg(NTf_2)_2$	*n*-Bu_4NPF_6	$MeNO_2$	20	90
11	$Ba(NTf_2)_2$	*n*-Bu_4NPF_6	$MeNO_2$	60	85
12	$Ca(NTf_2)_2$	*n*-Bu_4NBF_4	$MeNO_2$	10	86
13	$Ca(NTf_2)_2$	KPF_6	$MeNO_2$	10	91
14		*n*-Bu_4NPF_6	$MeNO_2$	60	

[a]Reaction conditions: **1** (1 equiv) and *p*-iodoaniline **2a** (1.1 equiv) in the indicated solvent (0.4 M) in the presence of catalyst (5 mol %) with/or without additive (5 mol %) at 80 °C. [b]1 mol % of catalyst and 1 mol % of additive. [c]On a gram scale of furan with 1 mol % of catalyst.

2 h to reach completion at 80 °C in $MeNO_2$ (entry 1). Gratifyingly, the expected product was isolated in 82% yield. On the other hand, with $Mg(NTf_2)_2$ and $Ca(NTf_2)_2$, full conversion was reached in 45 min and **3a** was isolated in 81% and 90% yield, respectively (entries 2 and 3). With $Ba(NTf_2)_2$, the product was obtained after 80 min in 84% yield (entry 4). 1,2-Dichloroethane (DCE) also proved to be a compatible solvent for the calcium-catalyzed reaction (entry 5), although the rate was lower. Interestingly, the use of the $Ca(NTf_2)_2$/*n*-Bu_4NPF_6 catalytic system in $MeNO_2$ resulted in a strong acceleration of the reaction and provided the desired product in only 10 min and 92% yield, best yield of the series (entry 6). The ammonium salt can actually promote an anion metathesis to form the heteroleptic complex $Ca(NTf_2)(PF_6)$, which, as shown recently,[13f] is more Lewis acidic than $Ca(NTf_2)_2$. This increase of the reaction rate was not observed in DCE, but the yield was also excellent (entry 7). While the aforementioned tests involved a 5 mol % loading of each catalytic component, it is worthy of note that the reaction is still very efficient with just 1 mol % (entry 8). In addition, the reaction can be run on a large scale, starting with 1 g of furan, albeit proceeding at a slower rate (entry 9). The acceleration effect provided by *n*-Bu_4NPF_6 was also observed with $Mg(NTf_2)_2$ and $Ba(NTf_2)_2$, but the transformation remained slower compared to calcium (entries 10 and 11). We examined also other additives with $Ca(NTf_2)_2$, such as *n*-Bu_4NBF_4 or KPF_6, which provided the same activity as *n*-Bu_4NPF_6 (entries 12 and 13). A control experiment using *n*-Bu_4NPF_6, in the absence of calcium, led to the recovery of the starting material (entry 14). Of note, the Lewis acids that have been previously used in Piancatelli reaction ($La(OTf)_3$, $Dy(OTf)_3$, $In(OTf)_3$), were proved as active as the calcium catalyst in the formation of **3a**, provided nitromethane is employed as solvent. In acetonitrile, which is the typical solvent for such transformations,[7] the rate is lower, especially with the lanthanide salts (see Table S1, Supporting Information).

We further explored the $Ca(NTf_2)_2$/*n*-Bu_4NPF_6 catalytic system for the reaction of 2-furyl(phenyl)methanol with various anilines (Table 2). A wide range of substituted anilines are

Table 2. Ca(II)-Catalyzed Cyclization of 2-Furyl(phenyl)methanol 1 with Anilines 2b–k[a]



1 **2b-k** **3b-k**

entry	R^1	R^2	temp (°C)	time (min)	yield (%)
1	H	C_6H_5	80	30	**3b** (90)
2	Me	C_6H_5	80	90	**3c** (82)
3	Allyl	C_6H_5	80	90	**3d** (76)
4	H	*p*-$MeOC_6H_4$	100	150	**3e** (81)
5	H	*p*-Tol	90	30	**3f** (75)
6	H	*p*-$MeO_2CC_6H_4$	80	20	**3g** (91)
7	H	*p*-NCC_6H_4	80	20	**3h** (74)
8	H	*m*-AcC_6H_4	90	120	**3i** (92)
9	H	*m*-IC_6H_4	80	20	**3j** (92)
10	H	*o*-IC_6H_4	80	20	**3k** (62)

[a]Reaction conditions: **1** (1 equiv) and aniline **2b–k** (1.1 equiv) in $MeNO_2$ (0.4 M) in the presence of $Ca(NTf_2)_2$ (5 mol %) and *n*-Bu_4NPF_6 (5 mol %) at the indicated temperature.

compatible with these conditions and afford the corresponding 4-aminocyclopentenones in high yields (up to 92%). *Ortho*, *meta*, and *para* substitution did not affect the reactivity (entries 4–10). The reaction is markedly slower with secondary anilines (entries 2 and 3). Anilines bearing an electron-donating group at the *para* position required temperatures higher than 80 °C to provide the corresponding 4-aminocyclopentenones (entries 4 and 5).

We then turned our attention to the substitution at the α position of the 2-furylcarbinols (Table 3). The reaction is not limited to an aryl substitution such as PMP (*p*-methoxyphenyl) (entry 1) but can be also carried out in the presence of an alkyl group (entry 2). Furthermore, in the presence of an allyl or a benzyl substituent, which have already been proven compatible with the Piancatelli reaction,[7i,14] the expected 4-amino-cyclopentenones were obtained as sole products in good yields (entries 3 and 4). Higher temperatures were required with the more sterically demanding substrates (entries 4 and 5).

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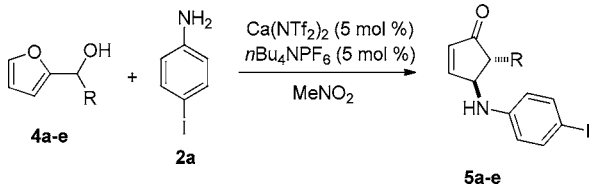
Table 3. Ca(II)-Catalyzed Cyclization of 2-Furylcarbinols 3a–e with *p*-Iodoaniline 2a[a]

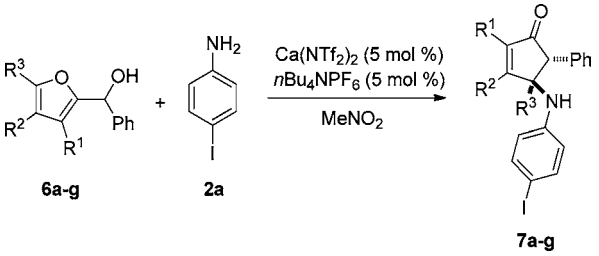


entry	R	temp (°C)	time (min)	yield (%)
1	PMP	40	10	**5a** (81)
2	Me	80	60	**5b** (80)
3	allyl	80	30	**5c** (86)
4	benzyl	100	60	**5d** (75)
5	$CH_2OTBDPS$	100	20	**5e** (58)

[a]Reaction conditions: **4a–e** (1 equiv) and aniline **2a** (1.1 equiv) in $MeNO_2$ (0.4 M) in the presence of $Ca(NTf_2)_2$ (5 mol %) and *n*-Bu_4NPF_6 (5 mol %) at the indicated temperature.

In the next set of experiments, we focused on the reactivity of 2-furyl(phenyl)methanol substituted at the furan ring (Table 4). In most cases, we noticed that the introduction of a substituent R^1 (entries 1–3) or R^2 (entries 4–6) did not hamper the reactivity. The 4-aminocyclopentenones were isolated in high yields (up to 97%). On the other hand, decomposition of the substrate was observed with a methyl group as R^3 (entry 7). This outcome might be the result of the steric hindrance, which could prevent the nucleophilic attack of the aniline on the oxonium intermediate.

Table 4. Ca(II)-Catalyzed Cyclization of Substituted 2-Furyl(phenyl)methanol 6a–g with *p*-Iodoaniline 2a[a]



entry	R^1	R^2	R^3	temp (°C)	time (min)	yield (%)
1	Me	H	H	80	20	**7a** (97)
2	Ph	H	H	90	20	**7b** (93)
3	Br	H	H	90	15	**7c** (93)
4	H	Me	H	90	30	**7d** (86)
5	H	Ph	H	80	20	**7e** (87)
6	H	Br	H	80	30	**7f** (65)
7	H	H	Me	80	60	**7g** (–)

[a]Reaction conditions: **6a–g** (1 equiv) and aniline **2a** (1.1 equiv) in $MeNO_2$ (0.4 M) in the presence of $Ca(NTf_2)_2$ (5 mol %) and *n*-Bu_4NPF_6 (5 mol %) at the indicated temperature.

In conclusion, we have shown that the aza-Piancatelli reaction can be catalyzed very efficiently by the easy-to-handle $Ca(NTf_2)_2$/*n*-Bu_4NPF_6 mixture. The use of the ammonium salt is not strictly necessary, but it significantly reduces the reaction time and improves the yields. This catalytic system has proven tolerant toward a broad range of substrates. Importantly, we have also shown for the first time that various substitution patterns at C2 and C3 of the furan ring can be used in the aza-Piancatelli reaction. Thus, a straightforward access to polyfunctionalized 4-aminocyclopentenones, which may serve as a platform for the synthesis of natural products such as those mentioned above has been developed.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all new 4-aminocyclopentenones. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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