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Microwave-assisted aza-Cope rearrangement of *N*-allylanilines

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Abstract

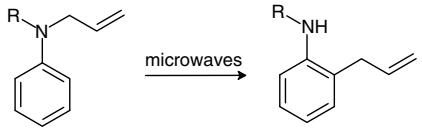
The aza-Cope rearrangement of *N*-allylanilines is described. The use of $BF_3{\cdot}OEt_2$ and microwave irradiation allows to run the transformation under mild conditions and in reaction times of minutes.

Keywords: Microwave; *N*-Allylaniline; Aza-Cope; Rearrangement

Among the most efficient reactions in terms of atom economy are the [3,3] sigmatropic shifts, that allow the formation of a C–C bond through the rearrangement of the molecule. While the Claisen rearrangement of vinyl and aryl allyl ethers has been extensively explored,[1] the nitrogen analogue of this reaction (aza-Cope rearrangement) has received much less attention due to several limitations. The rearrangement of aromatic *N*-allylamines is more difficult than that of the corresponding *O*-allylethers; thus the thermal uncatalyzed aza-Cope rearrangement requires temperatures ranging from 250 °C to 280 °C. Many of the reported procedures for this transformation call for the use of harsh reaction conditions, most of them requiring long reaction times and high temperatures. Usually, aromatic *N*-allylamines are not stable under these conditions, and significant amounts of anilines are formed by thermal decomposition. Some improvements have been achieved through the use of Lewis acids ($BF_3{\cdot}OEt_2$, $ZnCl_2$, $AlCl_3$)[2] and protic acids (HCl, H_2SO_4, *p*TsOH)[3] to decrease both temperature and reaction times, nevertheless the harsh reaction conditions limit the use of the aza-Cope rearrangement.

The use of microwave energy to directly heat chemical reactions has become one of the most popular techniques in the last few years.[4] But it has not been until very recently that its application has been claimed to facilitate [3,3] sigmatropic rearrangements of nitrogen-containing systems.[5] To the best of our knowledge, only one example of microwave-assisted aza-Cope rearrangement of allylanilines has been reported in the literature. A paper from Yadav et al.[6] called for the use of the microwave irradiation for the preparation of indolines from allylanilines, with the aid of montmorillonite as a catalyst. These compounds were formed by means of a [3,3] sigmatropic rearrangement, followed by in situ cyclization. However, the intermediate *ortho*-allyl anilines were not isolated, and its preparation was poorly described in the publication.

That prompted us to undertake a comprehensive study of the use of microwave-assisted reaction conditions for the transformation of *N*-allylanilines into *ortho*-allylanilines (Scheme 1), as these are quite interesting starting materials for the preparation of different bicyclic nitrogen-containing heterocycles through the cyclization of the nitrogen onto the double bond.[7]



Scheme 1.

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Table 1
Microwave-assisted reaction conditions screening

Entry	R	Solvent	Power (W)	T (°C)	Time (min)	Output
1	Boc	DMF	200	170	10	Deprotection
2	Boc	Xylenes	250	170	10	No reaction
3	H	Xylenes	290	170	10	No reaction
4	Ts	Xylenes	250	170	10	No reaction
5	Bn	DMF	250	170	10	No reaction
6	Bn	Toluene	250	125	10	No reaction
7	Bn	H_2O	100	120	10	No reaction
8	Bn	Xylenes	250	170	10	No reaction
9	Bn	Neat	290	160	10	10%
10	Bn	Xylenes[a]	220	170	10	30%
11	H	Xylenes[a]	290	170	10	Mixture
12	Ts	Xylenes[a]	290	170	10	No reaction

[a] $BF_3{\cdot}OEt_2$ was added to the reaction mixture.

Initially, we investigated the aza-Cope reaction of non-substituted *N*-allylanilines (Table 1), with different groups on the nitrogen (H, Boc, Ts and Bn). We found that in most of the cases no reaction took place when the compounds were submitted to microwave irradiation.[8] When *N*-Boc protected aniline was used, only deprotection products were isolated, and unreacted material was recovered when NH and N-tosylated precursors were irradiated for 10 min at 170 °C.

Only when neat N-benzylated *N*-allylaniline was irradiated, was the desired *ortho*-allyl aniline obtained in a 10% yield (entry 9). We then turned our attention to the use of Lewis acids as catalyst for this transformation. We found out that when 1 equiv of $BF_3{\cdot}OEt_2$ was added to the microwave vessel, the reaction rate was dramatically increased, to furnish the product in a 30% yield, with no starting material remaining unreacted (entry 10). When the same reaction conditions were applied to the NH analogue, a very complex mixture of products was obtained (entry 11). Once again, when the N-tosylated precursor was used no reaction was detected, and unreacted starting material was recovered (entry 12).

The reactivity of the different N-substituted compounds, suggests that the coordination of the Lewis acid to the nitrogen is a major factor of the process. While it is accelerating the reaction for the N-benzylated aniline, that is able to coordinate to the Lewis acid, no effect is observed for the less coordinating N-tosylated analogue. When the reaction was attempted over non-protected allylanilines, complex mixtures were obtained. Coordination of free anilines to the Lewis acid is stronger, and decomposition due to the generation of HF can occur.

Table 2
Catalyst screening

Entry	Catalyst	Conversion
1	$SnCl_2$	20%
2	$ZnCl_2$	6%
3	$Bi(OTf)_3$	78%
4	$BF_3{\cdot}OEt_2$	98%
5	$AlCl_3$	Loss of allyl
6	$TiCl_4$	Loss of allyl

With these results, we decided to further investigate the use of Lewis acids to catalyze the transformation (Table 2). Reactions were carried out using N-benzylated *N*-allyl aniline as the starting material, as it was the most promising substrate previously tested. The reactions were monitored by HPLC–MS and the conversion (as percent of product formed) was used as a comparative parameter.

Several Lewis Acids were able to promote the reaction. Among them, $BF_3{\cdot}OEt_2$ and $Bi(OTf)_3$ gave by far the best results. $ZnCl_2$ and $SnCl_2$ also facilitated the reaction, although with very low conversion. When stronger Lewis acids were used ($AlCl_3$ and $TiCl_4$), the only product isolated was that arising from the loss of the allyl group. We focused our efforts on the optimization of the $BF_3{\cdot}OEt_2$ catalyzed reaction, as this reagent is easy to handle, cheap and it was the catalyst that gave cleaner reactions.

Reaction conditions were then finely tuned in terms of reaction time, temperature and catalyst load (Table 3). The power seemed to have little influence on the reaction, and it was lowered from 290 W, used in the former experiments, to 200 W with no decrease in the reaction time or conversion.

The catalyst load could be lowered down to 0.5 equiv with no effects on conversion and reaction times (entries 1–3). When it was used in less than 15% mol, a drop in the conversion was observed. The reaction could be run even with lower loadings, and taken to completion, but longer reaction times were needed.

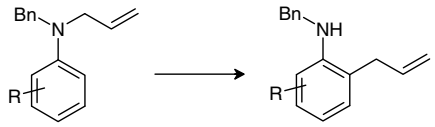
We found that the best temperature to run the reaction was above 150 °C. Complete conversion was always achieved at 170 °C, but longer reaction times or catalyst loadings were needed if reactions had to be run at lower temperatures.

Finally, we were gratified to find that, maintaining a catalyst load of 1.2 equiv, we could perform the reaction with complete conversion in as short times as 30 s (entry 10). It was observed that longer reaction times resulted in lower yield (entry 7), mainly due to the formation of by-products, arising from the decomposition of the *ortho*-allyl aniline.

When a sample of purified product was submitted again to the same reaction conditions, several products were formed. Two of these compounds were identified as cyclization products ($BF_3{\cdot}OEt_2$ also catalyzes the cyclization of the nitrogen by activating the allyl group), but some others were not characterized.

Table 3
Fine-tuning of the $BF_3{\cdot}OEt_2$ catalyzed reaction

Entry	Catalyst load	T (°C)	Time	Power (W)	Conversion (%)
1	1.2 equiv	170	5 min	290	98
2	0.75	170	5 min	290	98
3	0.5	170	5 min	290	98
4	0.15	170	5 min	290	60
5	1.2 equiv	150	5 min	290	85
6	1.2 equiv	135	10 min	290	30
7	1.2 equiv	170	10 min	220	30
8	1.2 equiv	170	2 min	200	98
9	1.2 equiv	170	1 min	200	98
10	1.2 equiv	170	30 s	200	98



Scheme 2.

To further explore the scope of the reaction, substitution on the aryl ring was investigated for different N-benzylated *N*-allyl anilines (Scheme 2, Table 4).[9] In general, most of the microwave-assisted reactions proceeded with good conversion within 1–2 min at 170 °C.[10] Again, excessive irradiation showed significantly diminished product yield with multiple uncharacterized by-products being formed.

Alkyl substitution is well tolerated (entries 1–4) even when the alkyl group is in the *ortho* position. When non-symmetrical substrates were irradiated, a non-separable mixture of both possible regioisomers was obtained in 1:1 ratio (entry 2). Electron rich groups are also well tolerated (entries 5 and 6), although in this case, when the group is located in the *ortho* position, lower yield was obtained due to the formation of several by-products (allyl loss was also detected). When the reaction was tried over halogen-bearing rings (entries 7 and 8), low yields were obtained due to the by-product formation. Entry 9 shows that strong electron withdrawing groups can be also present in the molecule, even with non-benzylated anilines, but the product is again obtained in low yield. It seems that these substrates are too reactive under the reaction conditions, and milder conditions should be developed to optimize the yield by minimizing the by-product formation.

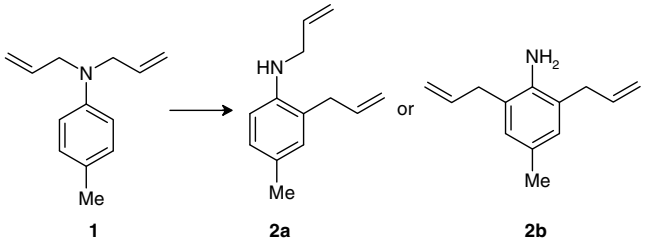
Quite interestingly, the reaction can also be run with N-bisallylated anilines (Scheme 3). Both allyl groups are transferred to the benzyl ring under usual reaction conditions to furnish **2b** in a 56% yield after purification. When the reaction is carried out under mild reaction conditions, it can be stopped when only one of the two allyl groups has migrated. Therefore, when a load of only 0.4 equiv of $BF_3{\cdot}OEt_2$ was used, and the reaction was allowed to react for only 1 min, **2a** was isolated in a 54% yield as the major reaction product.

In summary, a mild method for the [3,3] aza-Cope reaction of *N*-allyl anilines has been developed. The reaction can be carried out in minutes, which represents an improvement over current practices. Further application of this methodology for the preparation of bicyclic systems is currently under way in our laboratories.

Table 4
Substrate substitution studies

Entry	R	Yield (%)
1	2-Me	76
2	3-Me	50[a] (1:1)
3	4-Me	70
4	2,4-Me	72
5	2-OMe	30
6	4-OMe	64
7	2-F	21
8	2-I	38
9	2-NO_2	33[b]

Reaction conditions: xylenes, 170 °C, 200 W, 2 min.
[a] The reaction afforded a 1:1 mixture of regioisomers, that could not be separated by flash chromatography.
[b] Non-benzylated aniline was used.



Scheme 3.

Acknowledgement

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8. Experiments were carried out in a CEM Explorer microwave reactor, in a sealed vial applying a maximum power level of 290 W.
9. Substrates were prepared from commercially available anilines: they were *N*-benzylated by reductive amination with benzaldehyde, and then *N*-allylated by treating with allyl bromide and Cs_2CO_3 in DMF, to afford the products as colourless viscous oils.
10. To a solution of starting material (0.149 g, 0.63 mmol) in xylenes (1 mL) was added $BF_3{\cdot}Et_2O$ (0.09 g, 0.63 mmol). The mixture was irradiated in a CEM Explorer microwave reactor for 2 min at 170 °C and 290 W. The reaction was poured over saturated NH_4Cl solution (5 mL) and extracted twice with CH_2Cl_2. Organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified in a SP1 medium pressure chromatography equipment (column 25 + M, gradient of AcOEt/hexane from 0% to 15%) to yield 0.105 g (70%) of the product as a colourless oil.