

Reagent-free Nazarov cyclisations†

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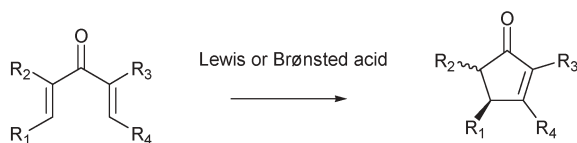
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A new protocol for Nazarov cyclisation is described that involves simple heating of dienones in the absence of any external Lewis acid.

The Nazarov cyclisation of dienones to produce 2-cyclopentenones has become one of the most powerful methods for cyclopentanulation in recent years (Scheme 1).^{1–10} Since its discovery in 1941,¹¹ the reaction has been subject to a steady stream of innovations such that the contemporary procedure delivers good yields of cyclopentenones under mild conditions, can operate with complete regiocontrol and displays reasonable functional group tolerance. In addition, the dienone substrates are easy to synthesise and the sound mechanistic picture that underpins the reaction permits the accurate prediction of substituent effects.

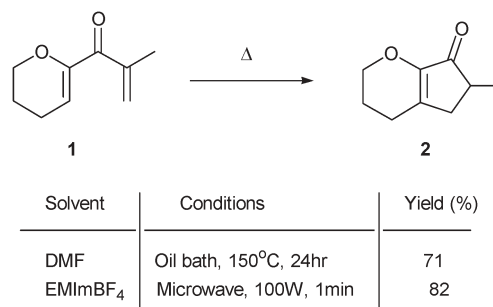


Scheme 1 The Nazarov cyclisation.

The development of progressively milder acid promoters has played an important role in the evolution of the Nazarov cyclisation as a versatile synthetic methodology. The original harsh, mineral acid promoters were largely superseded by strong Lewis acids such as AlCl_3 , SnCl_4 and FeCl_3 . Although generally effective, they were necessarily restricted to robust substrates that could tolerate the stoichiometric amounts of reagent that were usually required for complete reaction.¹ Recent reports in this area have described catalytic protocols for the cyclisation, as well as milder Lewis acids with non-nucleophilic counter-ions.^{2,3,5,8} In this report, we describe the Nazarov cyclisation of dienones in the absence of any acid promoters, producing a reagent-free transformation.

As part of a research program looking at new methods for cyclopentanulation, we noticed that the ketone **1** underwent thermal Nazarov cyclisation when heated in DMF, in the absence of any external acid. Despite the robust reaction conditions, the transformation was clean, producing the product cyclopentenone **2** in a respectable 71% yield (Scheme 2).

We were unaware of any precedent for Nazarov cyclisation in the absence of external acid promoters, and wanted to investigate



Scheme 2 Thermal Nazarov cyclisation of dienone **1** in the absence of added Lewis acid.

the generality of this transformation as a method for five-membered ring synthesis. Additionally, we were interested to see whether the electrocycloisatlon proceeds under simple thermal conditions; or whether an as-yet unidentified acidic component is acting as a catalyst for the process. With these two aims in mind, we began to optimise the reaction by replacing the conventional oil-bath heating conditions with microwave irradiation with a view to reducing the reaction time. A brief survey of reaction solvent indicated that polar aprotic solvents such as DMA or DMF worked well in the microwave, producing high yields of **2** after 15 min irradiation. DCM, methanol and acetonitrile were poor solvents for the reaction, producing none of the desired cyclopentenone. By far the best solvent, however, was the ionic liquid 1-ethyl-3-methylimidazolium tetrafluoroborate (EMImBF₄), giving an 82% yield of **2** after just 1 min of microwave irradiation. This, along with DMA, was chosen as the solvent to take forward for further study on the scope of this transformation with alternative substrates.

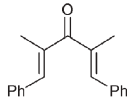
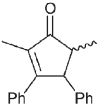
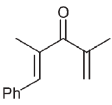
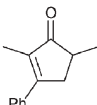
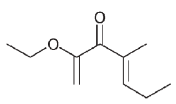
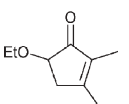
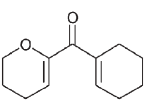
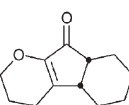
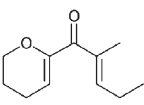
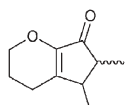
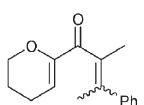
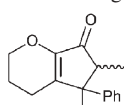
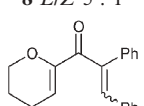
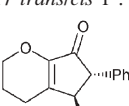
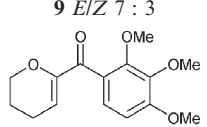
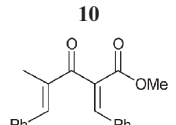
The dienones **3–11** were synthesised by literature methods¹² and subjected to thermal Nazarov cyclisation in EMImBF₄ or DMA, and the results shown in Table 1. We were pleased to observe the expected cyclopentenones being produced in good to excellent yields for a range of α,α' -dialkyl or oxyalkyl dienone substrates. Although EMImBF₄ produced some excellent yields of alkyl-substituted cyclopentenones in very short reaction times (entries 1 and 2), DMA proved to be the more versatile solvent overall. The reaction works well for cyclic and acyclic dienones, producing monocyclic (entries 1, 2 and 3), bicyclic (entries 5, 6 and 7) and tricyclic (entry 4) cyclopentanoid products. In all cases the cyclopentenone regioisomer having the most substituted double bond was the only isolated product from the reaction. We found disubstitution α - to the ketone group to be a necessary criterion for successful reaction, as both mono- and unsubstituted substrates failed to undergo ring closure. This substitution pattern is common in Nazarov substrates, and is thought to promote the population

† Electronic supplementary information (ESI) available: Synthetic procedures and characterisation data for all new compounds. See <http://www.rsc.org/suppdata/cc/b4/b415463k/>

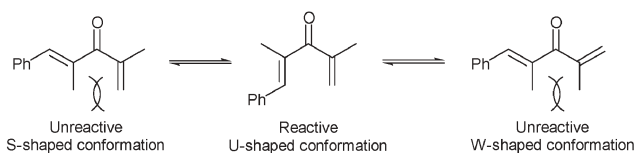
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Table 1 Thermal Nazarov cyclisations^a

Entry	Starting material	Product	Yield (%)
1 ^a			98
2 ^a			85
3 ^b			68
4 ^b			71
5 ^b			61
6 ^b			60
7 ^b			56
8 ^{a,b}		Recovered starting material	
9 ^{a,b}		Decomposition	

^a EMImBF₄; ^b DMA; see electronic supplementary information (ESI) for reaction details.

**Scheme 3** Conformational equilibrium illustrated for dienone **4**.

of the U-shaped conformation necessary for cyclisation by raising the energy of the unreactive S and W-shaped conformers (Scheme 3).^{4d} Substitution at the β-position by contrast is not as important (entries 2 and 3).

We synthesised dienone **8** with a view to examining possible alkyl shifts in the reaction, as β,β-disubstituted dienones are especially vulnerable to producing rearranged products under the acidic conditions of the classical Nazarov.¹³ Under the neutral conditions employed here, no such rearrangement products could be detected and the expected cyclopentenone **17** was produced smoothly in 60% yield. This moderate yield, and that of the diphenyl cyclopentenone **18**, is likely due to a failure of the minor Z-isomer in the starting dienones to undergo the desired ring closure. The requisite U-shaped conformation that the dienones must adopt for cyclisation is subject to severe steric hindrance in both **Z-8** and **Z-9**.

The reaction conditions could not be extended to all substrates. Ketone **10** (entry 8) was resistant to all attempts at achieving an aromatic Nazarov cyclisation, being recovered unchanged from the microwave vessel after prolonged irradiation. β-Keto esters such as **11** were also poor substrates, undergoing extensive decomposition under the microwave conditions.

The possibility of Brønsted acid catalysis was investigated by cyclising dienone **6** in freshly distilled DMA in the presence of one equivalent of proton sponge, using a base-washed microwave vessel. A slightly attenuated 60% yield was recorded, indicating that in DMA, genuine thermal cyclisation can occur in the absence of any acid catalysis. The success of the reaction in ionic liquids, by contrast, may in part be due to their weakly Lewis acidic character reinforcing their qualities as superb microwave solvents.^{14,15}

To conclude, we have discovered a new reagent-free protocol for Nazarov cyclisation that produces highly substituted cyclopentenones in good to excellent yields. In addition to the economic and environmental benefits of conducting reagent-free carbon-carbon bond formation, the neutral reaction conditions may enable the extension of Nazarov methodology to acid-sensitive substrates that have been previously inaccessible.

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