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Tetrahedron Letters 49 (2008) 2541–2545
Tetrahedron Letters

4-Toluenesulfonic acid: an environmentally benign catalyst for Nazarov cyclizations

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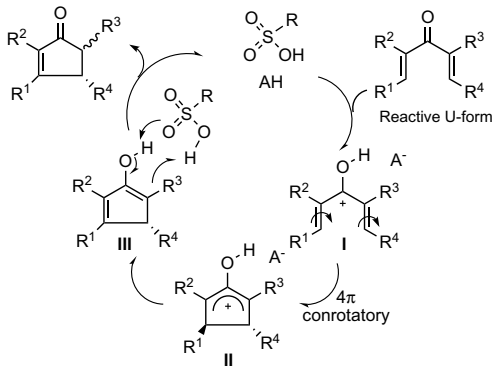
Received 1 February 2008; revised 14 February 2008; accepted 18 February 2008
Available online 21 February 2008

Abstract

An efficient metal-free catalytic protocol for the electrocyclization of α-alkoxydienones to cyclopentenones (Nazarov reaction) in near to quantitative yields is described. The key parameters are the use of inexpensive 4-toluenesulfonic acid in 5 mol % at room temperature in acetonitrile or under solvent-free conditions. The versatility of the transformation is demonstrated with unpolarized dienones with good regioselectivities and excellent yields.

Keywords: Nazarov reaction; Electrocyclic reactions; Enones; Organocatalysis; Sulfonic acids; Solvent-free reactions

Cyclopentenones are structural features frequently encountered in natural products.[1] The Nazarov reaction, which is the electrocyclization of conjugated dienones (divinyl ketones),[2] is a well-known and atom economic route to these structures. However, this methodology requires most often an acidic activation. Recently, a catalyst-free Nazarov reaction[3] has been described in ionic liquids under microwave heating. The high temperature used and the poor stereoselectivity limit such conditions to the rapid synthesis of simple cyclopentenones. Whereas Lewis acids have been successfully used under catalytic conditions, yielding cyclopentenones with excellent control of regioselectivity and enantioselectivity,[4] Brönsted acids either mineral or organic[5,6] require at least a stoichiometric amount to promote the electrocyclization. Surprisingly, only a few examples of Nazarov reaction using a catalytic amount of Brönsted acid (Scheme 1) have been reported to date. Neat damascenones were isomerized at 180 °C by TsOH (1%) into a mixture of compounds including the Nazarov product.[7] The same acid (0.5 equiv) in aromatic solvents and under reflux afforded hexahydroindenones from cyclohexenyl vinyl ketones.[8] TsOH (0.1 equiv) was also shown to be able to transform α′-hydroxyenones into cyclopentenones, although in moderate yields.[9] Recently, 10 mol % of TsOH was used to build, from conformationally favorable divinyl ketones, the five-membered ring of fusicoauritone.[10] Shindo et al.[11] reported the synthesis of 5-oxycyclopent-2-enones from β-alkoxy divinyl ketones catalyzed by TfOH (0.1 mol %), more efficient than TsOH.



Scheme 1. Mechanism for the Brönsted acid-catalyzed Nazarov reaction.

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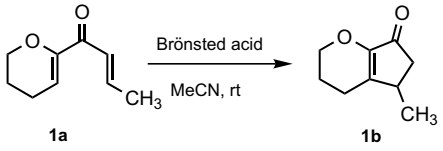
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.091

Finally Rueping et al.,[12] described the first enantioselective catalytic Nazarov reaction of α-alkoxy dienones. It was mediated by *N*-triflyl phosphoramides derived from BINOL. These results and the need for a simple, clean, and cheap organocatalyst for the Nazarov reaction prompted us to report our own results. We described here the efficient catalysis of the Nazarov electrocyclization, using 5 mol % of TsOH in organic solvents or under solvent-free conditions, of a variety of substrates, including unpolarized divinyl ketones.

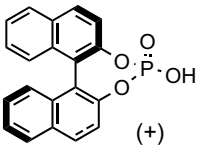
We first searched for a suitable and simple Brönsted acid catalyst for the Nazarov cyclization of dienone **1a** (Table 1). Sulfonic acids such as TsOH or (+)-CSA used in 20 mol % amount, in acetonitrile, transformed divinyl ketone **1a** into cyclopentenone **1b** in quantitative ^{1}H NMR yields after 3–4 h at room temperature (Table 1, entries 1–2). Optically pure (+)-CSA produced a racemic mixture of purified **1b**. TFA catalyzed the reaction too, but required a longer reaction time (entry 3). Cyclopentenone **1b** was obtained with picric acid although this catalyst was less efficient (entry 4). With less acidic compounds, the BINOL-derived phosphate[13] or aspartic acid, no product was detected in the reaction mixture (entries 5 and 6).

The previous results led us to optimize the solvent of the cyclization of dienone **2a** using TsOH as a catalyst decreasing its amount to 5 mol %. As shown in Table 2, a strong solvent effect was observed. Acetonitrile (entry 1), halogenated (entries 2–3) and aromatic solvents (entry 4) led to good to excellent yields of cyclopentenone **2b** at room temperature, whereas THF was not appropriate (entry 9). These results, except the one observed in acetonitrile, are in good agreement with the solvent effects reported in the electrocyclization of **2a** in the presence of BINOL-*N*-triflyl phosphoramide.[12] In other polar (acetone, DMF, entries 8 and 10), apolar (Et_2O, entry 7), or protic solvents (MeOH, EtOH, entries 5–6), the conversion was slower and lower yields of cyclopentenone **2b** were obtained, even after 24 h reaction time (entries 5–10). Finally, the reaction was carried out in the absence of any solvent (entry 11). The yield of cyclopentenone **2b** was similar to that obtained in acetonitrile (entry 1) but in a shorter reaction time. Hence, further Nazarov cyclizations were carried out in acetonitrile and under solvent-free conditions at room temperature.

Table 1
Evaluation of Brönsted acids in Nazarov cyclization

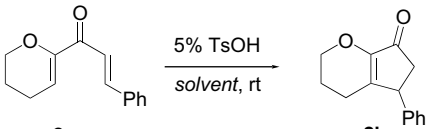


1a **1b**

Entry	Brönsted acid	Mol (%)	Time (h)	Yield[a] (%)
1	TsOH	20	3	100
2	(+)-CSA[b]	20	4	100
3	TFA	20	130	93
4	Picric acid	20	130	40
5		20	130	0
6	Aspartic acid	100	98	0

[a] Determined by ^{1}H NMR using 4,4′-di-*t*-butylbiphenyl as internal standard.
[b] CSA: camphorsulfonic acid.

Table 2
Solvent effect in the organocatalyzed Nazarov reaction



2a **2b**

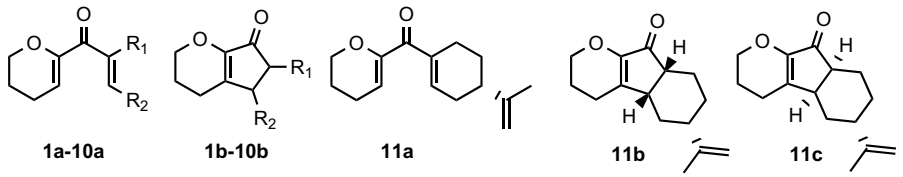
Entry	Solvent[a]	Time (h)	Yield[b] (%)
1	MeCN	15	94
2	$CHCl_3$	15	91
3	CH_2Cl_2	15	90
4	Toluene	15	85
5	MeOH	24	75
6	EtOH	24	40
7	Et_2O	24	25
8	Acetone	24	25
9	THF	24	10
10	DMF	24	10
11	No	4	89

[a] 1 mL/mmol.
[b] Isolated yields.

The scope of the reaction was then examined (Table 3). Various mono and disubstituted 2-alkoxy-1,4-pentadien-3-ones underwent cyclization smoothly to afford the corresponding cyclopentenones in yields higher than 80%.[14] In most of the cases, the reactions were clean and the product did not require any purification. As expected, the reactions were regioselective placing the double bond at the ring-junction with the dihydropyrane ring. The presence of a bulky substituent α to the carbonyl and a small or no substituent at the β position favor the reactive U-form of the dienone and thus the ring closure. The higher reactivity of dienones **10a** and **3a** compared, respectively, to those of **2a** and **4a** could be attributed to the presence of a phenyl group or of a double bond in β-position to the carbonyl enhancing the stabilization of the divinyl cation intermediate I (Scheme 1). The ring closure could also be accelerated by the release of the allylic strain in **3a** and the steric hindrance between the methyl and the phenyl in **10a**. The catalyst loading can be reduced to 1 mol % without significant change in reaction time, yield, and eventually diastereoselectivity as it was shown with substrates **7a** and **10a**. The higher reactivity of dienone **2a** in the Nazarov reaction under solvent-free conditions was confirmed with other substrates (entries 1, 3–11).

Particularly, the less reactive dienone **4a** afforded **4b** in 96% yield after 24 h whereas only 80% were obtained in

Table 3
TsOH-catalyzed Nazarov cyclization of α-alkoxy dienone **1a**–**11a**[a]



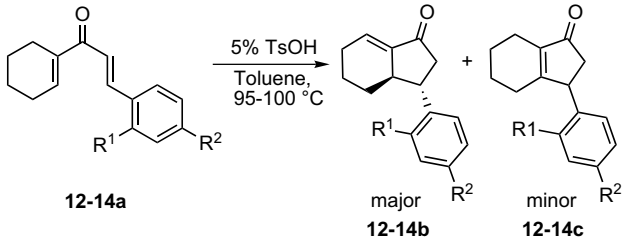
Entry	Products	R^1	R^2	MeCN, time (h)	Yield[b] (%)	*syn*/*anti*[c]	Neat, time (h)	Yield[b] (%)	*syn*/*anti*[c]
1	**1b**	H	Me	8	95		4	92	
2	**2b**	H	Ph	8	94		4	89	
3	**3b**	H	1-Propenyl	10	90		5	93	
4	**4b**	H	*n*-Pr	72	80		24	96	
5	**5b**	Me	H	4	97		2	97	
6	**6b**	*i*-Pr	H	3	98		2	97	
7[d]	**7b**	Bn	H	2	98		2	98	
8	**8b**	Me	Me	5	96	1.44:1	3	93	1.56:1
9	**9b**	Me	Et	4	97	3.35:1	2	97	3.54:1
10[d]	**10b**	Me	Ph	2	97	49:1	1	95	24:1
11	**11b**	—	—	4	93	1.44:1[e]	2	94	3.54:1[e]

[a] Reactions were carried out with 1 mmol of dienone, 5 mol % of TsOH at room temperature. 1 mL/mmol for the reactions carried out in MeCN.
[b] Isolated yields.
[c] *Syn* and *anti* isomers were identified by comparison with literature data and the ratio was determined by ^{1}H NMR.
[d] No change in the reaction efficiency was observed with 1 mol % of catalyst for substrates **7a** and **10a**.
[e] Diastereomeric ratio **11b**/**11c**.

acetonitrile after 72 h (entry 4). Diastereoselectivity was low for all disubstituted products except for **10b**. The high *syn* selectivity observed for this compound, higher to that previously reported (6:1),[12] could result from the kinetic protonation of intermediate **III** (Scheme 1) from the less hindered side of the enol.

The excellent yields for the Nazarov cyclization of alkoxy-activated substrates led us to attempt the reaction with unpolarized dienones **12a**–**14a** (Table 4). These compounds were conveniently prepared in good yields by the reaction of the lithium enolate of 1-acetylcyclohexene to the corresponding aldehydes.[4c] Reaction of **12a** with 5 mol % of TsOH in acetonitrile at 25 °C gave 26% of both regioisomers **b** and **c**, whereas heating to 95–100 °C in toluene led to mixture **12b**–**12c** in 86% yield (entries 1 and 2). The reaction was faster with substrate **13a** bearing an electron-enriched phenyl group at the β-position of the carbonyl group (2 h, 92% yield, entry 3), whereas with a 4-nitrophenyl substituent the cyclization of **14a** occurred with a lower rate (24 h, 82% yield, entry 4).[15] The major regioisomers **12b**–**14b** were the ones with the less substituted double bond. According to the conrotatory mode of cyclization and based on literature precedents,[2] we attributed a 3,4-*trans* relative stereochemistry to the substituents of cyclopentenones **12b**–**14b**. To our knowledge, only one example of catalyzed Nazarov reaction of unpolarized substrates such as **12a**–**14a** was described. It was mediated by a copper complex and the expected adducts were obtained in 30–42% yields.[16,17]

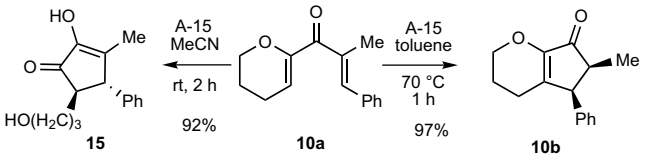
Table 4
TsOH-catalyzed Nazarov cyclization of unpolarized substrates



Entry	Dienone	R^1	R^2	Time (h)	Yield[a] (%)	**b**:**c**[b]
1	**12a**	H	H	24	26[c]	3.35
2	**12a**	H	H	10	86[d]	3.16
3	**13a**	OMe	OMe	2	92	5.25
4	**14a**	H	NO_2	24	82[e]	2.70

[a] Isolated yields of both regioisomers starting from 1 mmol of dienones.
[b] Ratio of the regioisomers measured after separation of each isomer by chromatography.
[c] The reaction was carried out at 25 °C.
[d] 6% starting material recovered.
[e] 12% starting material recovered.

Finally, with the aim of developing supported reagent based reactions,[18] commercially available resins functionalized by sulfonic acids were envisaged to catalyze the Nazarov reaction. Amberlyst-15 (A-15) was tested with divinyl ketone **10a** (Scheme 2).[19] In acetonitrile at room temperature the cyclization occurred rapidly followed by the opening of the dihydropyrane ring affording compound **15** in 92% yield. This compound has been recently obtained in the metal-catalyzed reaction.[4b] Heating **10a** in toluene at 70 °C in the presence of A-15 yielded Nazarov product **10b** quantitatively.



Scheme 2. Nazarov cyclization catalyzed by resin supported sulfonic acid.

In summary, we have shown that TsOH (5%) in acetonitrile or under solvent-free conditions exhibits a high catalytic performance for the Nazarov reaction of α-alkoxy dienones and unpolarized substrates. In many cases, the product obtained did not require any purification. This metal-free simple methodology, in which a cheap solid sulfonic acid was used, offers superior ecological viability over the often practiced Nazarov reactions conducted under drastic conditions and stoichiometric quantities of Brönsted acids. It should be compatible with the highly functionalized molecules, and thus attractive for the synthesis of complex natural products. The use of a polymer-supported catalyst (Amberlyst-15) afforded, in a preliminary experiment, either the Nazarov product or the 2-hydroxy-cyclopentenone, depending on the reaction conditions. Efforts to exploit this dual reactivity are underway. We are also currently developing chiral sulfonic acids for their application in enantioselective Nazarov cyclization.

Acknowledgments

We gratefully acknowledge the CNRS (Centre National de la Recherche Scientifique) for a fellowship to M.A., 'PunchOrga' Network (Pôle Universitaire Normand de Chimie Organique), 'Ministère de la Recherche et des Nouvelles Technologies', the 'Région Basse Normandie', and the European Union (FEDER funding) for funding. We are grateful to one referee for helpful comments.

References and notes

1. For a recent review, see: Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873–3890 and references cited therein.
2. For comprehensive reviews on Nazarov chemistry, see: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1–158; (b) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–442; (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206; (d) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606; (e) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517.
3. Douelle, F.; Tal, L.; Greaney, M. F. *Chem. Commun.* **2005**, 660–662.
4. For selected catalytic reactions, see: (a) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221–10228; (b) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927–4930; (c) Liang, G. X.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931–4934; (d) Aggarwal, V. K.; Beffield, A. J. *Org. Lett.* **2003**, *5*, 5075–5078; (e) Liang, G. X.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545; (f) West, F. G.; Lin, G. Y.; Yang, C. Y.; Liu, R. S. *J. Org. Chem.* **2007**, *72*, 6753–6757; (g) Nie, J.; Zhu, H. W.; Cui, H. F.; Hua, M. Q.; Ma, J. A. *Org. Lett.* **2007**, *9*, 3053–3056; (h) He, W.; Huang, J.; Sun, X. F.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 498–499 and references cited therein; (i) Bartali, L.; Larini, P.; Guarna, A.; Occhiato, E. G. *Synthesis* **2007**, 1733–1737; (j) Walz, I.; Bertogg, A.; Togni, A. *Eur. J. Org. Chem.* **2007**, 2650–2658.
5. For selected references of Brönsted acids used in Nazarov reactions, see H_3PO_4/HCO_2H: (a) Oda, M.; Yamazaki, T.; Kajioka, T.; Miyatake, R.; Kuroda, S. *Liebigs Ann. Rec.* **1997**, 2563–2566; (b) Kraft, P.; Cadalbert, R. *Synthesis* **2002**, 2243–2253; polyphosphoric acid: (c) Minami, T.; Nakayama, M.; Fujimoto, K.; Matsuo, S. *J. Chem. Soc., Chem. Commun.* **1992**, 190–191; $HClO_4$: (d) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613–616; $HClO_4/Ac_2O$: (e) Fernandez Mateos, A.; Martin de la Nava, E. M.; Rubio Gonzalez, R. *Tetrahedron* **2001**, *57*, 1049–1057; (f) Fernandez Mateos, A.; Mateos Buron, L.; Martin de la Nava, E. M.; Rubio Gonzalez, R. *J. Org. Chem* **2003**, *68*, 3585–3592; HCl: (g) Casson, S.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1187–1191; (h) Cheng, K. F.; Cheung, M.-K. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1213–1218; H_2SO_4: (i) Clive, D. L. J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954–961; CF_3CO_2H: (j) Ishikura, M.; Imaizumi, K.; Katagiri, N. *Heterocycles* **2000**, *53*, 2201–2219; (k) Hiyama, T.; Shinoda, M.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 771–774.
6. (a) Ogura, K.; Arai, T.; Kayano, A.; Akazome, M. *Tetrahedron Lett.* **1998**, *39*, 9051–9054; (b) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774–6780; (c) Oda, M.; Kajioka, T.; Haramoto, K.; Miyatake, R.; Kuroda, S. *Synthesis* **1999**, *8*, 1349–1353; (d) Kajioka, T.; Oda, M.; Yamada, S.; Kawamori, Y.; Miyatake, R.; Kuroda, S. *Synthesis* **1999**, *1*, 184–187; (e) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380–1381.
7. Ohloff, G.; Schulte-Elte, K. H.; Demole, E. D. *Helv. Chim. Acta* **1971**, *54*, 2913–2915.
8. Wada, E.; Fujiwara, I.; Kanemasa, S.; Tsuge, O. *Bull Soc. Chim. Jpn* **1987**, *60*, 325–334.
9. (a) Jacobson, R. M.; Lahm, G. P. *J. Org. Chem.* **1979**, *44*, 462–464; (b) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395–405.
10. Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 915–918.
11. Shindo, M.; Yaji, K.; Kita, T.; Shishido, K. *Synlett* **2007**, 1096–1100.
12. Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097–2100.
13. The phosphoric acid derivative was prepared from optically pure BINOL. The Nazarov reaction was performed in refluxing acetonitrile. However, beside degradation compounds, less than 10% yield of **1b** was obtained. Therefore, the enantiomeric excess was not measured.
14. *General procedure for the Nazarov cyclization of 2-alkoxy-1,4-pentadien-3-ones* **1a**–**11a**. TsOH (10 mg, 0.05 mmol, 5 mol %) was added to 2-alkoxy-1,4-pentadien-3-one (1.0 mmol) either neat or in CH_3CN (1.0 mL). The reaction mixture was flushed with nitrogen and was stirred at room temperature until the disappearance of starting material (TLC monitoring). After completion, the crude product was dissolved in diethyl ether (50 mL) and washed with aqueous $NaHCO_3$ (15 mL). After separation, the organic layer was washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. Most of the substrates gave clean reactions and no purification was needed. When required, the purification was carried out by flash column chromatography (8–10% of EtOAc in cyclohexane).
15. *General procedure for the Nazarov cyclization of α,β-dialkyl-β′-aryl-divinyl ketones* **12a**–**14a** (unpolarized substrates). TsOH (10 mg, 0.05 mmol, 5 mol %) was added to divinyl ketone **12a**–**14a** (1.0 mmol) in toluene (1.5 mL). The reaction mixture was flushed with nitrogen and was heated at 100 °C until the disappearance of starting material (TLC monitoring). After completion of the reaction, the crude product was dissolved in EtOAc (50 mL) and washed with aqueous $NaHCO_3$ (15 mL). After separation, the organic layer was washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated

under vacuum. Regioisomers **b** and **c** were separated by flash column chromatography (silica gel, EtOAc/cyclohexane).

16. (a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279; (b) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011.
17. Under iridium catalysis, a substrate similar to **13a** did not cyclize due to the stabilization of its unreactive S-form, see: Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 6864–6865.
18. For a 'Fully automated multi-step solution phase synthesis using polymer-supported reagents', see: Vickerstaffe, E.; Warrington, B. H.; Ladlow, M.; Ley, S. L. *Org. Biomol. Chem.* **2003**, *1*, 2419–2422.
19. For an example of Nazarov reaction catalyzed by A-15, see: Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728–9741 and references cited therein.