Tetrahedron Letters 54 (2013) 6258–6263

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mild conversion of propargylic alcohols to α,β-unsaturated enones in ionic liquids (ILs); a new 'metal free' life for the Rupe rearrangement

Ganesh C. Nandi, Benjamin M. Rathman, Kenneth K. Laali *

Department of Chemistry, University of North Florida, 1 UNF Drive, Jacksonville, FL 32224, USA

ARTICLE INFO

Article history:
Received 7 August 2013
Revised 3 September 2013
Accepted 10 September 2013
Available online 18 September 2013

Keywords:
Conjugated enones
Propargylic alcohols
Metal free Rupe rearrangement
Imidazolium ionic liquids
Recycling/reuse
Rupe–Aldol–Nazarov sequence

ABSTRACT

A mild and selective transition metal free protocol for the conversion of propargylic alcohols to cyclic and acyclic α,β-unsaturated enones via the Rupe rearrangement is reported. The method utilizes the Brønsted acidic ionic liquid [BMIM-SO_3H][OTf] as catalyst and [BMIM][PF_6] as solvent and offers the potential for recycling and reuse of the IL solvent. The feasibility to synthesize bicyclic fused cyclopentenone derivatives via a Rupe → Aldol → Nazarov sequence utilizing this protocol has also been demonstrated.

Synthesis of α,β-enones and α,β-enals via formal isomerization of propargylic alcohols represents an attractive, atom-economical, approach that provides direct access to these highly versatile synthetic building blocks.[1–3] Propargylic cations are key intermediates involved in these transformations. Whereas trapping (by H_2O) of the mesomeric allenyl cations (γ-substitution) leads to the Meyer–Schuster rearrangement products (enones or enals), β-elimination (when applicable) triggers the Rupe rearrangement, forming an enyne and subsequently the enone. These mechanistic pathways are outlined in Scheme 1.

The traditional protocols employed in the Meyer–Schuster and Rupe reactions typically involve the use of large quantities of strong Brønsted acids, and consequently suffer from low chemoselectivity and poor yields.[4] The utility of Nafion-H as a solid acid catalyst for the Rupe rearrangement was shown in representative cases.[5] During the last decade a number of transition metal-based methods were discovered for the conversion of propargylic alcohols to enones and enals. These include rhodium/BINAP complex,[6] allyl-ruthenium(II) complex/TFAH,[7] rhenium(V)-oxo complex,[8] and an oxovanadate complex under microwave.[9] A number of gold-catalyzed processes have also been reported including [(NHC)AuCl]AgX,[10] $Ph_3PAuNTf_2$,[11] and a triazole-coordinated Au(I) complex.[12] A carbonyl-rhenium complex formed by coordination of iminophosphorane-phosphane ligands to [$ReBr(CO)_5$] was shown to be quite active for the Rupe isomerization under microwave irradiation in ionic liquid solvent.[13] Except for the works reported in Refs. 7 and 13, the primary focus of the aforementioned studies has been the Meyer–Schuster reaction.

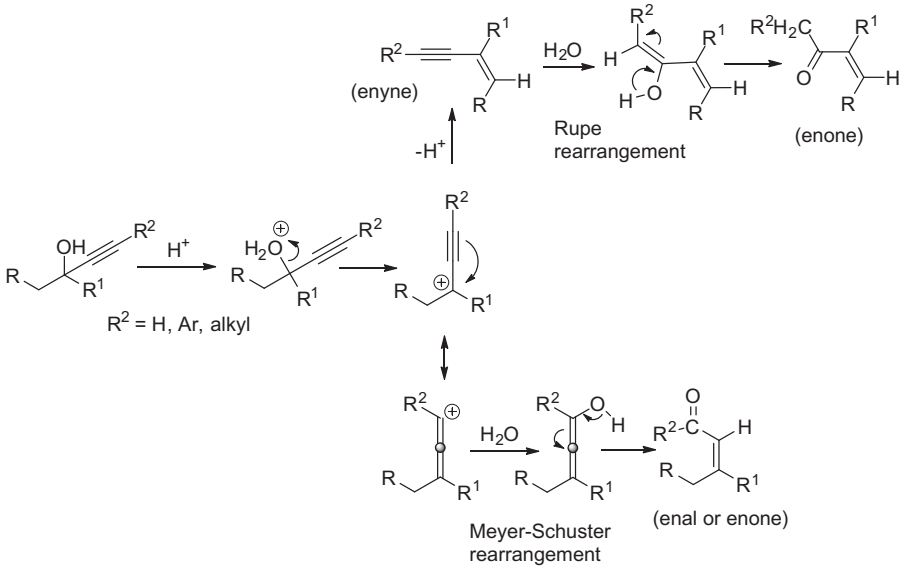
Despite considerable progress that has been achieved through transition-metal catalysis, there is a need to develop readily available, low cost, methods that also offer potential for recycling and reuse. In relation to our continuing interest in the utility of ionic liquids as catalysts and solvents for synthetic carbocation and onium ion chemistry,[14] and our more recent focus on generation and synthetic utility of tamed propargylic cations,[15] we report here on a transition metal free, IL-based, method for the selective conversion of propargylic alcohols to α,β-unsaturated enones via the Rupe reaction.

Optimization studies were performed by using 1-ethynylcyclohexanol **1a** as a test substrate (Table 1). Whereas acceptable isolated yields of the enone could be obtained after 3 days at room temperature, optimal conversions were achieved at 50 °C in less than an hour by employing 30 mol % of [BMIM-SO_3H][OTf].

These conditions were then adopted in a subsequent survey of the scope of the reaction (Table 2).[16] Monitoring the progress of the reactions (TLC) showed that tweaking of the reaction times was necessary depending on the substrates in order to achieve optimal conversions. It is noteworthy that competing Meyer–Schuster products were not detected in these reactions. Reaction of propargylic alcohol **1e** resulted in the expected enone **2e** along

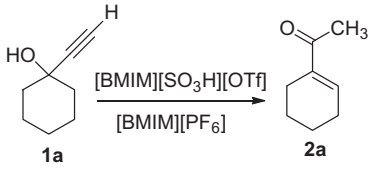
* Corresponding author. Tel.: +1 904 620 1503; fax: +1 904 620 3535.
E-mail address: Kenneth.laali@UNF.edu (K.K. Laali).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.028



Scheme 1. Divergence between the Rupe and the Meyer–Schuster Rearrangements.

Table 1
Optimization of the reaction conditions

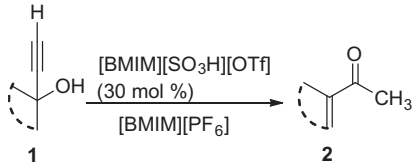


1a **2a**

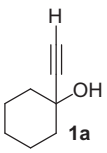
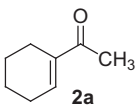
Entry	Catalyst (mol %)	Time	Temp (°C)	Yield[a] (%)
1.	20	3 day	25	56
2.	30	3 day	25	62
3.	40	3 day	25	60
4.	20	65 min	50	78
5.	**30**	**50** min	**50**	**84**
6.	40	50 min	50	82
7.	30	45 min	75	81

[a] Isolated yield.

Table 2
Conversion of ethynylalkanols to conjugated enones via the Rupe reaction

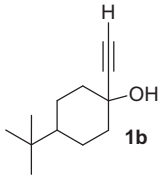
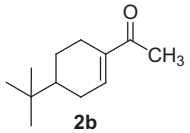
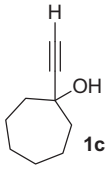
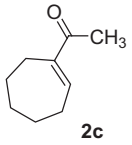
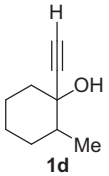
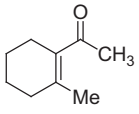
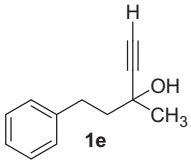
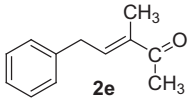
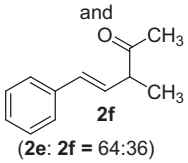
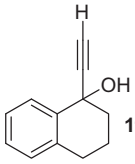
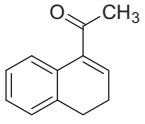


1 **2**

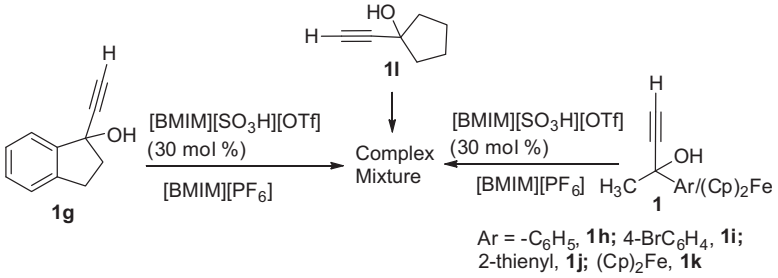
Entry	Ethynylalkanol (**1**)	Conjugated enone (**2**)	Time/Yield[a] (%)
1.	 **1a**	 **2a**	50 min/86

(*continued on next page*)

Table 2 (*continued*)

Entry	Ethynylalkanol (**1**)	Conjugated enone (**2**)	Time/Yield[a] (%)
2.	 **1b**	 **2b**	60 min/87
3.	 **1c**	 **2c**	75 min/82
4.	 **1d**	 **2d**	2 h/76
5.	 **1e**	 **2e** and  **2f** (**2e**: **2f** = 64:36)	3 h/45
6.	 **1f**	 **2g**	2 h/48

[a] Isolated yield.



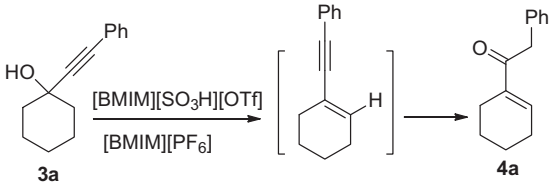
Scheme 2. Formation of complex mixtures with α-aryl, α-ferrocenyl, and α-cyclopentyl derivatives.

with a structural isomer **2f**. Lower conversions were obtained with propargylic alcohols **1e** and **1f**. The *trans* stereochemistry in **2e** was established based on NOE (in Supplementary data).

Extension of the survey study to α-aryl (**1h**; **1i**; **1j**) and α-ferrocenyl (**1k**) alkynols resulted in complex mixtures (Scheme 2). The contrasting behavior of the cyclohexyl (**1a** and **1f**) and the cyclopentyl derivatives (**1g** and **1l**), with the latter giving rise to complex mixtures, is surprising.

Focusing attention on the phenylethynyl-derivatives, phenylethynylcyclohexanol **3a** was employed as a test substrate for an optimization study (Table 3). Runs 1–3 resulted in isolation of the corresponding enyne, presumably because of the higher stability of the phenylpropargyl cation. The Rupe product was isolated in acceptable yield employing a higher catalyst loading (2.5 equiv) at 75 °C after 5 h. Competing formation of the Meyer–Schuster rearrangement products was not observed.

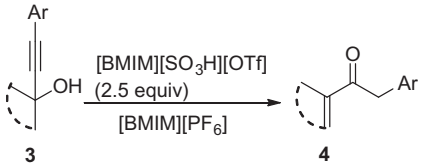
Table 3
Optimization of the reaction with phenylethynylcyclohexanol **3a**

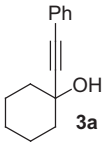
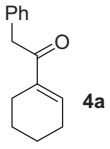
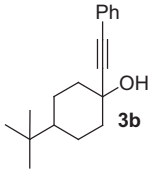
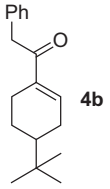
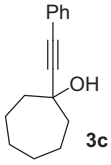
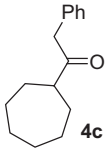
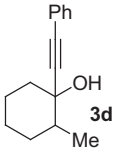
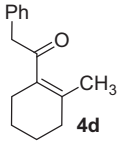
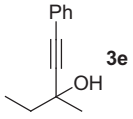
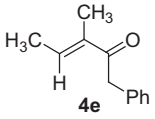


Entry	Catalyst (equiv)	Time (h)	Temp (°C)	Yield[a] (%)
1.	0.3	24	50	[b]
2.	0.3	24	75	[b]
3.	1.0	24	75	[b]
4.	**2.5**	**5**	**75**	**48**
5.	3.0	5	75	43

[a] Isolated yield.
[b] Enyne was isolated.

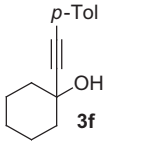
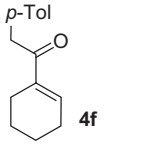
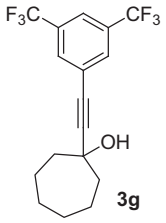
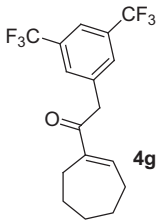
Table 4
Conversion of arylethynylalkanols to conjugated enones via the Rupe reaction



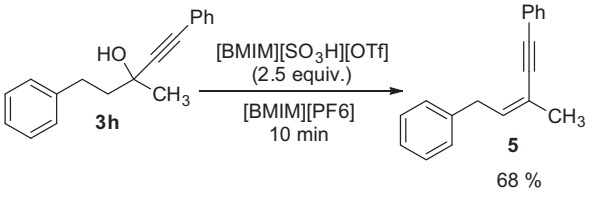
Entry	3	4	Time (h)/Yield[a] (%)
1.			5/48
2.			7/54
3.			5/45
4.			6/8
5.			4/41

(*continued on next page*)

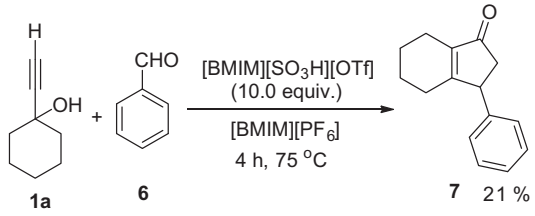
Table 4 (*continued*)

Entry	3	4	Time (h)/Yield[a] (%)
6.			5/51
7.			6/39

[a] Isolated yield.



Scheme 3. Isolation of enyne **5** from **3h**.



Scheme 4. The Rupe → Aldol → Nazarov sequence in IL.

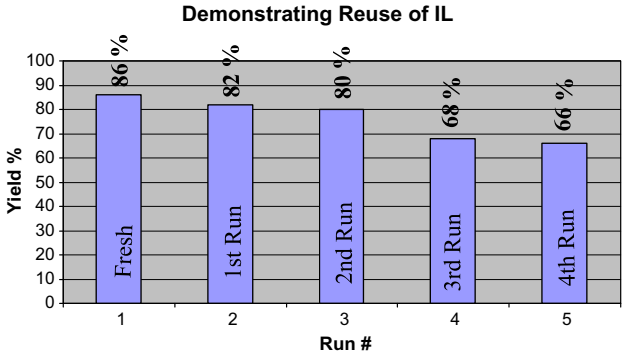
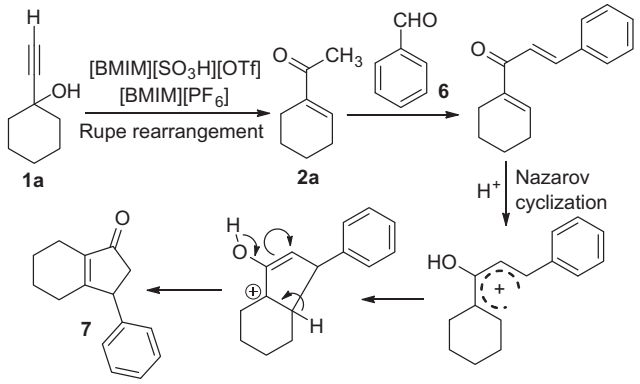


Chart 1. Recycling of [BMIM][PF_6] for reaction with 1-ethynylcyclohexanol (**1a**).



Scheme 5. Mechanistic steps for the Rupe → Aldol → Nazarov transformations leading to compound **7**.

The scope of this transformation was then investigated by employing arylethynylalkanols **3a**–**3g** with 2.5 equiv of Brønsted acidic IL (Table 4).[17] The reaction times were tweaked in each case for optimal conversion. Isolated yields of the Rupe products varied from 54% to 8% depending on the substrate. The *trans* stereochemistry in **4e** was established based on NOE (Supplementary data).

The phenylpropargyl alcohol **3h** reacted quickly to form the enyne **5** which was isolated in good yield. Attempts to transform the enyne to enone by prolonged heating (24 h at 75 °C) led to a complex mixture (see Scheme 3).

The recycling and reuse of [BMIM][PF_6] solvent was investigated for the Rupe reaction of 1-ethynylcyclohexanol (**1a**) in four consecutive runs by simply vacuum drying the IL at 70 °C for about 12 h and re-using it in successive runs after addition of fresh Brønsted acid IL. The results summarized in Chart 1 indicate a gradual decrease in the isolated yields from 86% to 66%.

In the context of the present study, and in connection to a 2010 report on one-pot synthesis of cyclopentenone derivatives via a Rupe → Aldol → Nazarov sequence employing a 16-electron allylruthenium(II) pre-catalyst in large excess of TFAH (50 mol %)[18] we examined the feasibility to carry out a transition metal free version of this chemistry in IL. When ethynylcyclohexanol **1a** was reacted with benzaldehyde **6** employing only 1.0 equiv of [BMIM][SO_3H][OTf] a complex reaction mixture resulted. By increasing the Brønsted acidic IL to 10 equiv, phenylindenone **7** was isolated in 21% yield (Scheme 4).[19] The structure of compound **7** was confirmed by its reported analytical data.[20]

The mechanistic steps involving the in-situ formation of the enone (Rupe product), Aldol condensation with benzaldehyde, followed by a Nazarov cyclization, are sketched in Scheme 5.

In summary, an ionic liquid-based protocol for the one-pot synthesis of α,β-enones from a diverse set of cyclic and acyclic propargylic alcohols has been developed, utilizing [BMIM-SO_3H][OTf] as catalyst and [BMIM][PF_6] as solvent. Study of the scope of the reac-

tion shows considerable promise but also some limitations. The feasibility to synthesize bicyclic fused cyclopentenone derivatives via a Rupe → Aldol → Nazarov sequence utilizing this protocol is also notable. The present transition metal free approach represents a new life for the Rupe rearrangement.

Acknowledgment

We thank the University of North Florida for research support.

Supplementary data

Supplementary data (detailed procedures for the synthesis of ethynylalkanols and phenylethynyl alkanols and the analytical data (NMR, MS, IR) for the products obtained in this study are gathered in the accompanying Supplementary data file) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.028.

References and notes

1. Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149–4158.
2. Cadierno, V.; Crochet, P.; Garcia-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015–4031.
3. Bauer, E. B. *Synthesis* **2012**, *44*, 1131–1151.
4. Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429–438.
5. Olah, G. A.; Fung, A. P. *Synthesis* **1981**, 473–474.
6. Tanaka, K.; Shoji, T. *Org. Lett.* **2005**, *7*, 3561–3563.
7. Cadierno, V.; Garcia-Garrido, S. E.; Gimeno, J. *Adv. Synth. Catal.* **2006**, *348*, 101–110.
8. Stefanoni, M.; Luparia, M.; Porta, A.; Zanoni, G.; Vidari, G. *Chem. Eur. J.* **2009**, *15*, 3940–3944.
9. Antinolo, A.; Carrillo-Hermosilla, F.; Cadierno, V.; Garcia-Alvarez, J.; Otero, A. *ChemCatChem* **2012**, *4*, 123–128.
10. Ramon, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767–1773.
11. Pennell, M. N.; Turner, P. G.; Sheppard, T. D. *Chem. Eur. J.* **2012**, *18*, 4748–4758.
12. Wang, D.; Zhang, Y.; Harris, A.; Gautam, L. N. S.; Chen, Y.; Shi, X. *Adv. Synth. Catal.* **2011**, *353*, 2584–2588.
13. Garcıa-Alvarez, J.; Diez, J.; Gimeno, J.; Seifried, C. M. *Chem. Commun.* **2011**, 6470–6472.
14. See for example: (a) Aridoss, G.; Laali, K. K. *Eur. J. Org. Chem.* **2011**, 2827–2835; (b) Laali, K. K.; Okazaki, T.; Bunge, S. D. *J. Org. Chem.* **2007**, *72*, 6758–6762; (c) Kalkhambkar, R. G.; Waters, S. N.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 867–871.
15. See for example: (a) Aridoss, G.; Sarca, V. D.; Ponder, J. F., Jr.; Crowe, J.; Laali, K. K. *Org. Biomol. Chem.* **2011**, *9*, 2518–2529; (b) Kumar, G. G. K. S. N.; Kumar, K. K. Laali *Org. Biomol. Chem.* **2012**, *10*, 7347–7355; (c) Kumar, G. G. K. S. N.; Aridoss, G.; Laali, K. K. *Tetrahedron. Lett.* **2012**, *53*, 3066–3069; (d) Kumar, G. G. K. S. N.; Laali, K. K. *Tetrahedron. Lett.* **2013**, *54*, 965–969; (e) Aridoss, G.; Laali, K. K. *Tetrahedron. Lett.* **2011**, *52*, 6859–6866.
16. *General procedure for the synthesis of Rupe rearrangement products* ***2a–g***: the ethynyl alcohol **1** (0.5 mmol) was added to [BMIM][PF_6] (2 ml, 20 equiv) in a Schlenk tube and [BMIM][SO_3H][OTf] (30 mol %) was introduced at rt with stirring. The reaction mixture was stirred at 50 °C for the specified period of time (see Table 2). After completion of the reaction (TLC monitoring), the reaction mixture was extracted several times with 30% ethyl acetate in hexane (25 ml) and the combined organic extracts were washed with aq saturated $NaHCO_3$ followed by water, dried ($MgSO_4$), and evaporated. The crude product was purified by preparative TLC.
17. *General procedure for the synthesis of Rupe rearrangement product* ***4a–g***: the phenylethynyl alcohol **3** (0.5 mmol) was added to [BMIM][PF_6] (2 ml, 20 equiv) in a small Schlenk tube and [BMIM][SO_3H][OTf] (2.5 equiv) was introduced at rt with stirring. The reaction mixture was stirred at 75 °C for the indicated period of time (see Table 4). After completion of reaction (TLC monitoring), the reaction mixture was extracted several times with 30% ethyl acetate in hexane (25 ml) and the combined organic extracts were washed with aq saturated $NaHCO_3$ followed by water, dried ($MgSO_4$), and evaporated. The crude product was purified by preparative TLC.
18. Cadierno, V.; Gimeno, J.; Nebra, N. *ChemCatChem* **2010**, *2*, 519–522.
19. *General procedure for the synthesis of phenylindenone* ***7***: the 1-ethynylcyclohexanol **1a** (0.5 mmol) and benzaldehyde **6** (0.5 mmol) were mixed with [BMIM][PF_6] (15 equiv) in a small Schlenk tube and [BMIM][SO_3H][OTf] (10.0 equiv) was then introduced. The reaction mixture was stirred at 75 °C for 4 h. After completion of reaction, the reaction mixture was extracted several times with 40% ethyl acetate in hexane (40 ml) and the combined organic extract was washed with aq saturated $NaHCO_3$ followed by water, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography using 7% ethyl acetate in hexane as eluent.
20. Caruana, P. A.; Frontier, A. J. *Tetrahedron* **2007**, *63*, 10646–10656.