Heterocyclic Synthesis

International Edition: DOI: 10.1002/anie.201510729
German Edition: DOI: 10.1002/ange.201510729

Harnessing the Electrophilicity of Keteniminium Ions: A Simple and Straightforward Entry to Tetrahydropyridines and Piperidines from Ynamides

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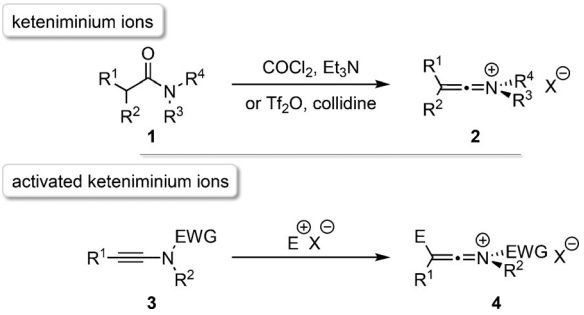
Abstract: *An efficient, modular and straightforward entry to tetrahydropyridines and piperidines is reported. This reaction is based on a formal intramolecular hydroalkylation of readily available, properly substituted ynamides which, upon simple activation under acidic conditions, generate highly reactive activated keteniminium ions whose reactivity can be finely controlled to induce a remarkably efficient [1,5]-hydride shift from unactivated C–H bonds and trigger a cationic cyclization which is complete within minutes.*

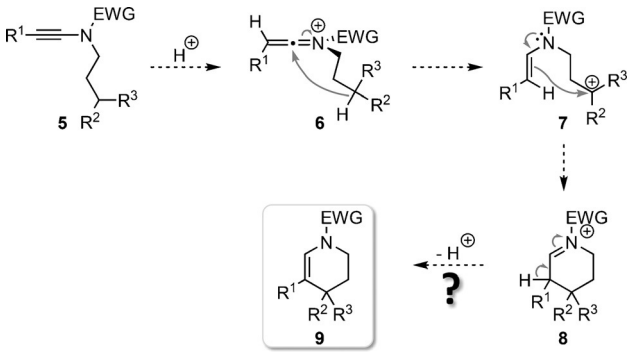
Provided that they can be easily generated from readily available, simple starting materials, highly reactive intermediates enable the design of remarkably efficient reactions whose successful outcome entirely relies on the peculiar reactivity of these short-lived, high-energy molecules. The exploration of their chemistry has been an especially fruitful approach in chemical synthesis, which resulted in the development of an impressive number of original and efficient processes,[1] one of the most representative example certainly lying in Olah's work on the chemistry of carbocations.

Among other cationic reactive intermediates, keteniminium ions **2**, which are conveniently prepared from *N*,*N*-dialkylamides **1** (Scheme 1), have proven to be an especially useful subclass.[2] Their inherent peculiar reactivity could be elegantly exploited for the design of remarkable transformations such as the [2+2] cycloaddition with alkenes developed by Ghosez.[3] Trapping these highly electrophilic heterocumulenes with suitably functionalized nucleophiles could also be used to trigger, in most simple manners and utmost efficiency, a range of reactions[4] whose synthetic utility has been highlighted by the Maulide group.[2b] Besides these "classical" keteniminium ions **2**, even more reactive analogues **4** bearing an electron-withdrawing group on the nitrogen atom have been recently investigated. Indeed, such intermediates—which are conveniently obtained from readily available ynamides **3**[5] and electrophiles—have been shown to be incredibly electrophilic species.[6] Provided that this exceptional level of reactivity can be finely tuned and controlled, it can be used to promote reactions in which simple keteniminium ions **2** fail and, notably, to activate poorly reactive C–H bonds through hydride abstraction or hydrogen shift.[6k,7]



Scheme 1. Classical (**2**) and activated (**4**) keteniminium ions.

In this context, we recently reported that activated keteniminium ions were indeed reactive enough to initiate a [1,5]-sigmatropic hydrogen shift from an unactivated benzylic position, which triggered a cationic polycyclization reaction.[6k] Based on these results, we envisioned that a [1,5]-hydride shift[8] might also be feasible starting from a suitably functionalized keteniminium ion such as **6**, which could be simply generated by protonation of the corresponding ynamide **5** (Scheme 2). Provided that this hydride shift would be operative,[9] selective, and faster than the trapping of the keteniminium ion with either its counter-anion or the starting ynamide, a carbocation **7** would be generated, which



Scheme 2. Reaction design for the keteniminium-triggered intramolecular hydroalkylation of ynamides.

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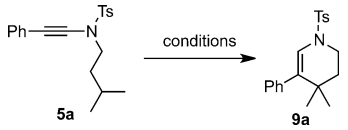
Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201510729.

could then, hopefully, react intramolecularly with the enamide moiety formed after the hydride shift. Further elimination of a proton from cyclic iminium ion **8** would then give the functionalized tetrahydropyridine **9** resulting from a formal intramolecular hydroalkylation of the starting ynamide **5**.[10]

As part of our ongoing program on the chemistry of ynamides[11] and motivated by the easy access to highly substituted piperidine derivatives—a privileged scaffold both in natural-product and medicinal chemistry[12]—that this route might provide, we decided to evaluate the feasibility of this intramolecular hydroalkylation.

To test our hypothesis and, if successful, optimize the reaction, model ynamide **5a**, possessing an isopentyl chain suitably placed to favor the [1,5]-hydride shift, was selected. A strong acid, triflic acid, was chosen to promote the reaction in order to avoid trapping of the highly reactive keteniminium ion by the conjugated base which should be as poorly nucleophilic as possible. The first trial turned out to be actually rather successful since upon treatment of **5a** with ten equivalents of triflic acid in dichloromethane at 0 °C, the desired cyclized product **9a** was formed within 15 min in 41 % yield (Table 1, entry 1). The reaction was in fact faster than initially anticipated since it could be performed at −78 °C or −60 °C, which in addition resulted in a net improvement of the yield.[13] The amount of triflic acid could be reduced to five equivalents without affecting the efficiency of the process (Table 1, entry 4) while the use of two equivalents caused a significant decrease of the yield (Table 1, entry 5). Attempts to reduce the amount of acid further or to use catalytic amounts of bis(trifluoromethanesulfone)imide resulted in much lower yields (Table 1, entries 6–9), which could be attributed to the complete protonation of the cyclized product **9a** under the reaction conditions.[14] Interestingly, scandium or gold complexes, which are known to be good π-activators, were found to be totally inefficient (Table 1, entries 10–12).

Table 1: Validation of the working hypothesis and optimization of the reaction.



Entry	Conditions	Yield [%][a]
1	TfOH (10 equiv), 0 °C, 15 min	41
2	TfOH (10 equiv), −78 °C, 15 min	67
3	TfOH (5 equiv), −78 °C, 15 min	68
4	TfOH (5 equiv), −60 °C, 15 min	66
5	TfOH (2 equiv), −60 °C, 15 min	59
6	TfOH (1 equiv), −60 °C, 15 min	4
7	TfOH (1 equiv, reverse addition), −60 °C, 15 min	6
8	Tf_2NH (25 mol %), −55 °C, 12 h	0
9	Tf_2NH (25 mol %), RT, 24 h	0
10	$Sc(OTf)_3$ (5 mol %), RT, 12 h	0
11	$(Ph_3P)AuNTf_2$ (5 mol %), RT, 3 h	0
12	$IPrAuNTf_2$ (5 mol %), RT, 3 h	0

[a] Yield determined by NMR spectroscopy using tetrachloroethane as an internal standard.

As a note, an activated keteniminium ion is required for the reaction to proceed since replacing the tosyl group in **5a** by an alkyl chain did totally suppress the hydride shift.[15]

Having demonstrated the feasibility of the hydride-shift/cyclization sequence, we then moved to the study of the scope and limitations of this reaction.[16] We initially focused on the reactivity of ynamides **5a**–**n** bearing an isopentyl chain, α-substituted or not (Figure 1). Upon reaction with triflic acid in dichloromethane at −60 °C for 15 min, most of these ynamides were smoothly converted to the corresponding tetrahydropyridines in fair to good yields. Among the sulfonyl groups evaluated, the reaction was found to be compatible with tosyl (**9a**), nosyl (**9b**), and mesyl (**9c**) protection on the nitrogen atom, the latter being superior in terms of yield. The reaction proceeded well with various aromatic substituents on the starting ynamides, the efficiency being directly correlated with the electron density on the aromatic ring. Indeed, electron-poor aryl groups gave the corresponding cyclized products **9d** and **9e** in good yields while the reaction was found to be less efficient when increasing the electron density on the aromatic ring. A methyl substituent was still tolerated (**9f**) while a strongly donating methoxy substituent afforded the cyclized product (**9g**) in only 15 % yield, which can be

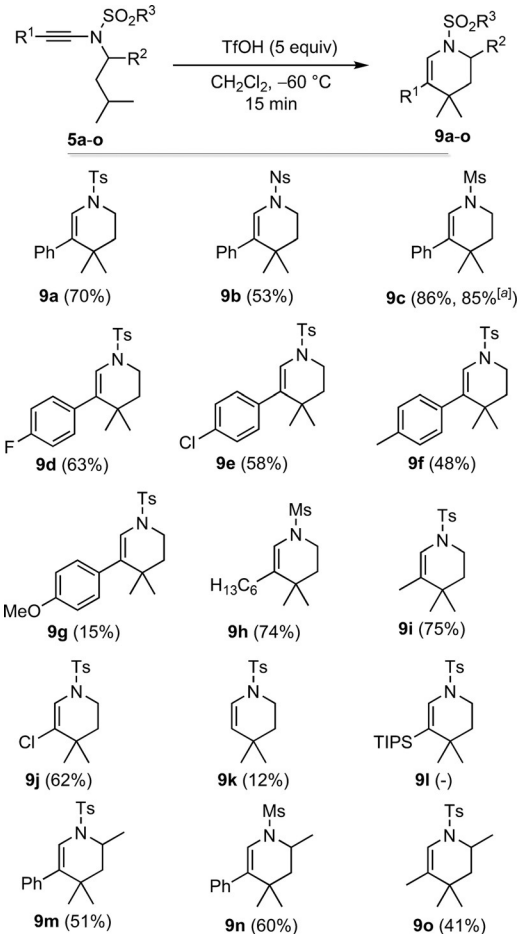
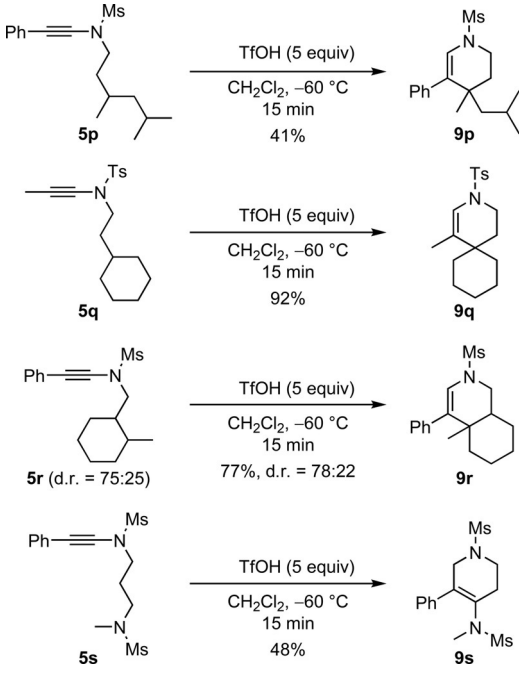


Figure 1. Scope and limitations of the intramolecular hydroalkylation of *N*-isopentylynamides. [a] Reaction performed on a 1.5 g scale.

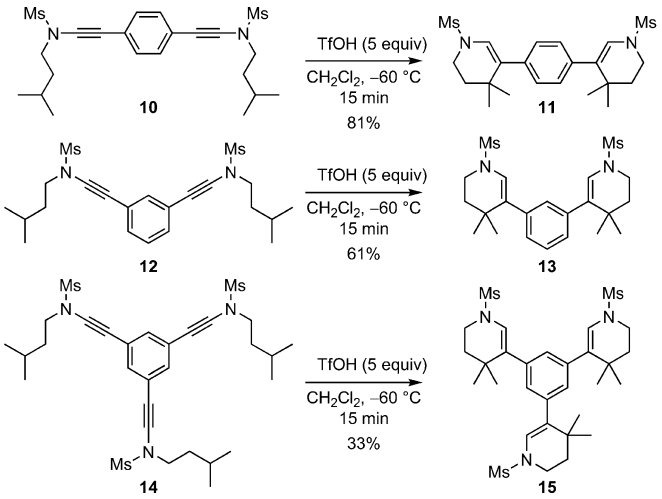
attributed to competitive protonation of the aromatic ring under the reaction conditions or lower reactivity of the corresponding keteniminium ion—as also noted starting from a TIPS-substituted ynamide (**5l**). Scaling up the reaction did not affect the yield since the cyclization could be conveniently conducted on a 1.5 g scale without altering its efficiency (see **9c** in Figure 1). Gratifyingly, the reaction still performed nicely in the presence of alkyl chains to yield the tetrahydropyridines substituted with hexyl (**9h**) or methyl (**9i**) groups at C3 in 74% and 75% yield, respectively. A chlorinated ynamide could also be readily cyclized to **9j**, therefore providing opportunities for further functionalization. Not surprisingly, a rather labile terminal ynamide did not survive the reaction conditions and gave the cyclized product **9k** in only 12% yield. Finally, the presence of an additional substituent on the isopentyl chain did not affect the cyclization as demonstrated with the synthesis of tetrasubstituted tetrahydropyridines **9m–o**.

Investigation of the influence of the chain from which the hydride is transferred revealed that the reaction can be extended to the preparation of tetrahydropyridines with other substitution patterns and increased complexity. Indeed, the presence of an additional substituent at the end of the isopentyl chain enabled the introduction of two different substituents at the C4 position, such as in **9p** (Scheme 3), and the introduction of a cyclohexyl group provided an efficient access to spirocyclic compounds such as **9q**. Moving the cyclohexyl ring along the side chain allowed for a different connectivity between the two ring systems since an isoquinoline skeleton (**9r**) was now formed during the hydride-shift/cyclization sequence. Finally, ynamide **5s** bearing a suitably protected propylamine chain could also be readily cyclized to **9s** in which the double bond was isomerized during the process.[17]



Scheme 3. Variation of the hydride-donor chain: increasing the molecular complexity.

To further test the efficiency of the cyclization and push it to its limits, we next investigated the possibility of performing double and triple cyclizations. To this aim, bis-ynamides **10** and **12** and tris-ynamide **14** were synthesized and subjected to our optimized conditions (Scheme 4). To our greatest pleasure, the bis-ynamides **10** and **12** were readily cyclized to the corresponding bis-tetrahydropyridines **11** and **13** in 81% and 61% yields, respectively, which delineates the potential of this keteniminium-triggered cyclization. The triple hydroalkylation was a bit more complex due to the competing hydrolysis of **14**. The triply cyclized product **15** could however be isolated in 33% yield, which still represents a decent 70% yield per cyclization.



Scheme 4. Double and triple hydride-shift/cyclization sequences.

Finally, aiming at introducing an additional substituent on the piperidine ring, we envisioned trapping the intermediate iminium ion **8** (Scheme 2) by a nucleophile. Logically, and in accordance with previously reported results,[6] when this nucleophile is added at the beginning of the reaction, it directly reacts with the keteniminium ion before the hydride shift can occur. Knowing that the tetrahydropyridine was fully protonated (to **8**) under the reaction conditions,[14] we surmised that the nucleophile would be best added after the cyclization. To our delight, this strategy turned out to be quite efficient and indeed allowed for an efficient synthesis of highly substituted piperidines **16** (Figure 2). The use of 1,3-dimethoxybenzene as a nucleophile introduced an aryl substituent at the C2 position of the ring, such as in **16a**/**a′** and **16b**. In these compounds, the relative configuration of the piperidine formed was interestingly found to depend on the nature of the starting ynamide, the cyclization of **5a** and **5c** yielding the *trans* piperidine **16a**/**a′** while the *cis* isomer **16b** was formed starting from **5j**.[18] While the use of indole derivatives failed to provide the corresponding piperidines, a 2-cyanopiperidine (**16c**) could be efficiently prepared in good yield and useful level of selectivity upon addition of TMSCN after the cyclization. Moreover, triethylsilane cleanly reduced the intermediate iminium to afford piperidines **16d–f** with substituents at C3 and C4 only.

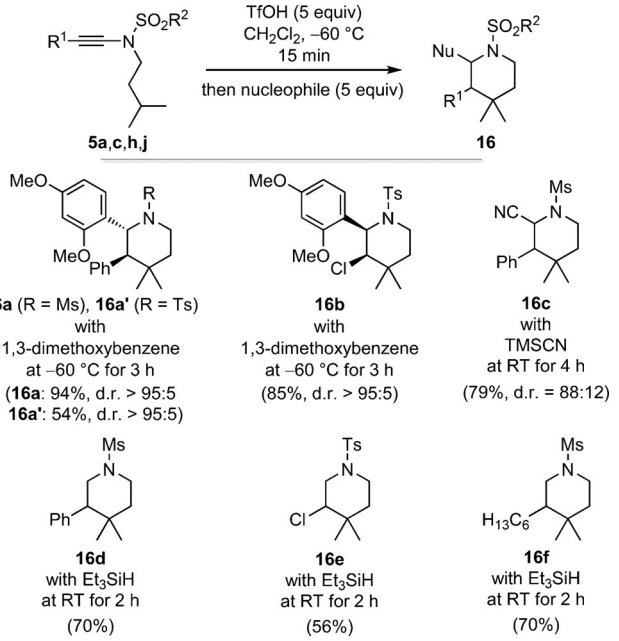


Figure 2. Trapping the intermediate iminium ion **8** with a nucleophile: a straightforward entry to highly functionalized piperidines.

In conclusion, we have demonstrated that by using the proper substitution pattern the reactivity of activated keteniminium ions can be finely harnessed so that they can initiate a [1,5]-hydride shift from unactivated C–H bonds. This reactivity could be exploited for the design of a hydride-shift/cyclization sequence providing a straightforward, modular, and divergent access to tetrahydropyridines and piperidines in a single operation and with a high atom economy. The broad availability of the starting ynamides and the simple protocol needed for their cyclization are notable features of this reaction. In addition to the use of this formal intramolecular hydroalkylation in heterocyclic chemistry, this study brings new insights into the chemistry of ynamides and keteniminium ions.

Acknowledgements

Our work was supported by the Université libre de Bruxelles (ULB) and the FNRS (Incentive Grant for Scientific Research n° F.4530.13). M.L. acknowledges the Fonds pour la formation à la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A.) for a graduate fellowship. The authors also thank Prof. Michel Luhmer (ULB) for his assistance with NMR studies and are indebted to Sofia Kajouj and Julien Van Liefferinge for their precious technical assistance.

Keywords: cationic cyclizations · hydride shift · keteniminium ions · piperidines · ynamides

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4547–4551
Angew. Chem. **2016**, *128*, 4623–4627

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[17] The replacement of the MeMsN unit in **5s** by a methoxy group led to a totally different outcome since the corresponding ynamide was fully hydrolyzed to an amide under the reaction conditions.

[18] The relative configurations of piperidines **16a**/**a′** and **16b** were assigned on the basis of the values of the $^{3}J_{H_2,H_3}$ coupling constants and NOESY experiments (see the Supporting Information for details). An unambiguous rationalization of their diastereoselective formation cannot be proposed at present. The relative configuration of the major diastereomer of **16c** could not be unamiguously determined.

Received: November 19, 2015
Revised: February 4, 2016
Published online: March 2, 2016

