ORGANIC LETTERS

2012
Vol. 14, No. 22
5728–5731

Efficient Synthesis of α,β-Unsaturated Alkylimines Performed with Allyl Cations and Azides: Application to the Synthesis of an Ant Venom Alkaloid

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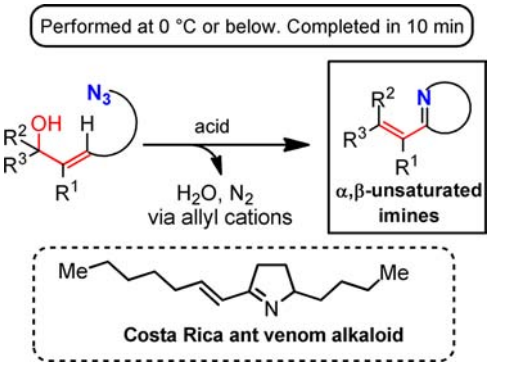
Received October 4, 2012

ABSTRACT



An efficient synthesis of α,β-unsaturated alkylimines at low temperature using azides has been developed. Carbocations generated from allyl alcohols helped achieve a rapid conversion under mild conditions with azides to afford reactive α,β-unsaturated imines. Hydroxy or alkoxy groups are essential for these transformations, and utilizing readily accessible allyl alcohols gave a wide extension of substrates. The efficiency of this novel method is demonstrated in the total synthesis of an iminium ant venom alkaloid.

α,β-Unsaturated imines (1-aza-1,3-butadienes, enimines) provide more useful synthetic efficiency than saturated imines, for example, as Michael acceptors, hetero-Diels–Alder diene units, and dienophiles.[1,2] Despite their usefulness and their simple structures, the preparation of α,β-unsaturated imines, especially alkyl and cyclic enimines, is problematic due to the tendency toward polymerizations and hydrolysis by strong reactivity. Simple condensation of α,β-unsaturated carbonyls and amines is often carried out, but mostly to produce *s-trans*-fixed α,β-unsaturated alkylimines.[1e,f] Thus, some elimination strategies have been developed, but their heating conditions should be avoided for the reactivity of products (Scheme 1a).

Furthermore, azides can also deliver saturated imines.[4] The Schmidt reaction with alcohols or olefins and azides

(1) For recent examples, see: (a) Tanaka, K.; Siwu, E. R. O.; Hirosaki, S.; Iwata, T.; Matsumoto, R.; Kitagawa, Y.; Pradipta, A. R.; Okumura, M.; Fukase, K. *Tetrahedron Lett.* **2012**, *53*, 5899–5902. (b) Hachiya, I.; Mizota, M.; Shimizu, M. *Heterocycles* **2012**, *85*, 993–1016. (c) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 4064–4067. (d) Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 4785–4787. (e) Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G. A.; Evans, D. A. *Org. Lett.* **2011**, *13*, 3758–3761. (f) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 3997–4000. (g) Hong, B.-C.; Wu, J.-L.; Gupta, A. K.; Hallur, M. S.; Liao, J.-H. *Org. Lett.* **2004**, *6*, 3453–3456.

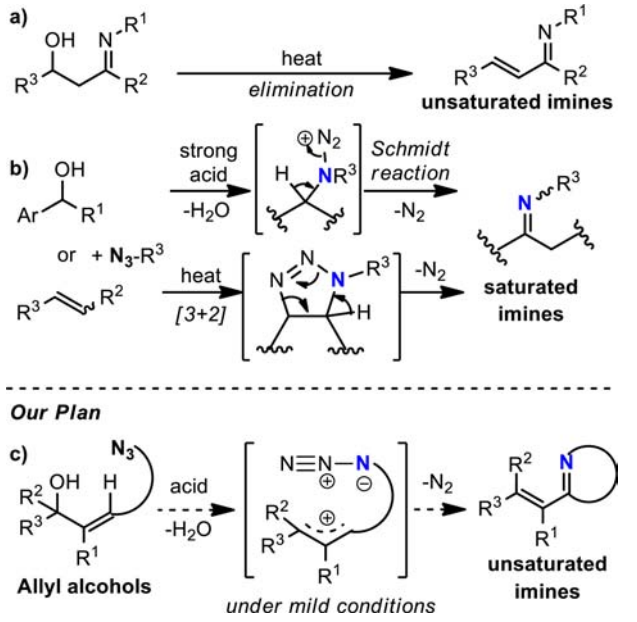
(2) (a) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138. (b) Fletcher, M. D.; Hurst, T. H.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2006**, *62*, 5454–5463. (c) Kobayashi, S.; Furuya, T.; Otani, T.; Saito, T. *Tetrahedron* **2008**, *64*, 9705–9716. (d) Chen, W.-S.; Fowder, F. W.; Lupo, A. T., Jr. *J. Am .Chem. Soc.* **1981**, *103*, 2090–2091. (e) François, D.; Maden, A.; Murray, W. V. *Org. Lett.* **2004**, *6*, 1931–1934. (f) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035–6041. (g) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713–1729.

(3) Schuster, E.; Hesse, C.; Schumann, D. *Synlett* **1991**, 916–918 and references therein.

10.1021/ol302608q
Published on Web 11/01/2012

gives corresponding saturated imines via aminodiazonium intermediates (Scheme 1b).[5] However, this requires strong acids and the substrates are limited to benzyl alcohols and styrenes to generate carbocations.[5d,e] Although simple olefins can also produce saturated imines with azide by way of [3 + 2] cyclization, high temperatures (> 100 °C) and long reaction times (from several hours to days) are required.[6] Moreover, direct transformation to "unsaturated" imines through these procedures is quite limited.[7,8] Thus, a more efficient method is required.

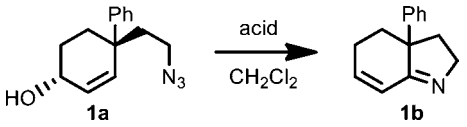
Scheme 1. Preparation of Imines and Our Plan



Our research plan is shown in Scheme 1c. To achieve a rapid one-step transformation to unsaturated imines under mild conditions, we envisioned that allyl cations that are easily accessible from allyl alcohols in the presence of weak−moderate acids could help our desired reactions to produce α,β-unsaturated imines. Despite the reported reactions of azides with oxyallylic and benzylic cations that produce [3 + 2] and [3 + 3] reaction products,[5f−h] unsaturated imine synthesis from allyl cations with azides has not been reported. Focusing on these advantages of the allylic carbocation, herein we report a fast, efficient intramolecular transformation from azide-bearing allylic alcohols to α,β-unsaturated imines under mild conditions and its application to the total synthesis of an ant venom alkaloid.

Since the desired unsaturated alkylimines were anticipated to be unstable due to hydrolysis or their ability as a diene for the hetero Diels−Alder reaction, we commenced our study with the cyclic substrate **1a** which could afford a rigid bicyclic unsaturated imine **1b**, similar to the molecule in the report from Pearson's group.[6e]

Table 1. Screening of Reaction Conditions



entry	acid[a]	T (°C)	time	yield (%)[b]
1	TFA	reflux	60 min	trace
2	$TsOH \cdot H_2O$	reflux	30 min	96
3[c]	TFA	rt	20 min	69
4	$TsOH \cdot H_2O$	rt	2 days	27
5	MsOH	0	40 min	58
6	TMSOTf	0	10 min	86
7	none	reflux	60 min	n.r.

[a] 1.2 equiv of acid were used except for entry 3. [b] Isolation yield. [c] 22 equiv were used. TFA = trifuluoroacetic acid, TsOH = *p*-toluenesulfonic acid, MsOH = methanesulfonic acid, n.r. = no reaction.

Optimizations of acids and temperature conditions with allyl alcohol **1a** were attempted in dichloromethane (Table 1). Although trifluoroacetic acid (pK_a = 12.65 in CH_3CN)[9] produced a trace amount of **1b** under reflux (entry 1), *p*-toluenesulfonic acid (pK_a = 8.45 in CH_3CN) completed the reaction in 30 min to afford desired **1b** in excellent yield (entry 2). It is noteworthy that the synthesis of this unsaturated imine was accomplished with a moderate acid at around 40 °C within 1 h, despite previous reports indicating

(4) (a) Bräse, S.; Banert, K. *Organic Azides, Syntheses and Applications*; John Wiley & Sons: Ltd.: Chichester, 2010. (b) Wrobleski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2012**, *78*, 1–320. (c) Chiba, S. *Synlett* **2012**, *23*, 21–44. (d) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247–12275. (e) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240.

(5) (a) Banerjee, A.; Kumar, P. S.; Baskaran, S. *Chem. Commun.* **2011**, *47*, 12218–12220. (b) Pearson, W. H.; Fang, W. K. *J. Org. Chem.* **2000**, *65*, 7158–7174. (c) Molina, P.; Alcántara, J.; Leonardo, L. *Synlett* **1995**, 363–364. (d) Pearson, W. H.; Fang, W. K. *J. Org. Chem.* **1995**, *60*, 4960–4961. (e) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickendorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194. For other examples of a reaction between azides and Oxy(or amino)allyl cations including a cyclization reaction, see: (f) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114–117. (g) Grecian, S.; Desai, P.; Mossman, C.; Poutsma, J. L.; Aubé, J. *J. Org. Chem.* **2007**, *72*, 9439–9447. Pearson et al. also reported intramolecular [3 + 2] and [3 + 3] cyclization with indolic *tert*-carbocations to give triazolines and triazines rather than imines. See: (h) Pearson, W. H.; Fang, W. K.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682–2684. For an S_N2-type Schmidt reaction, see: (i) Kapat, A.; Nyfeler, E.; Giuffredi, G. T.; Renaud, P. *J. Am. Chem. Soc.* **2009**, *131*, 17746–17747.

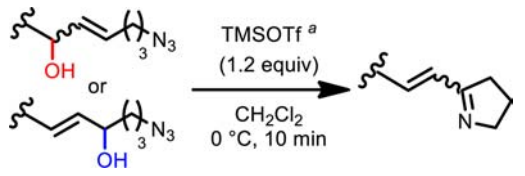
(6) (a) de Miguel, E.; Valedo, M.; Herradón, B.; Mann, E. *Eur. J. Org. Chem.* **2012**, 4347–4353. (b) Zhao, Y.-M.; Gu, P.; Tu, Y.-Q.; Zhang, H.-J.; Zhang, Q.-W.; Fan, C.-A. *J. Org. Chem.* **2010**, *75*, 5289–5295. (c) Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10*, 3777–3780. (d) Kim, S.; Lee, Y. M.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886–4891. (e) Schkeryantz, J.; Pearson, W. H. *Tetrahedron* **1996**, *52*, 3107–3116. (f) Hudlicky, T.; Luna, J. H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683–4687. (g) Reddy, D. S.; Judd, W. R.; Aubé, J. *Org. Lett.* **2003**, *5*, 3899–3902.

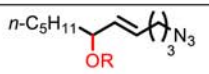
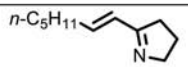
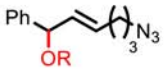
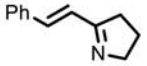
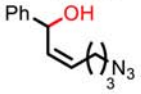
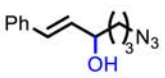
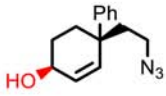
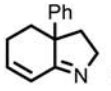
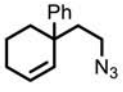
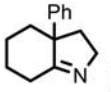
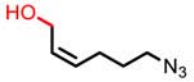
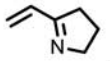
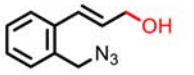
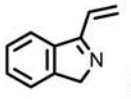
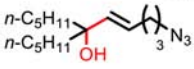
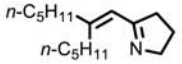
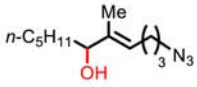
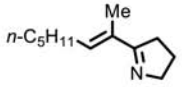
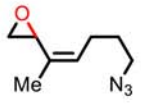
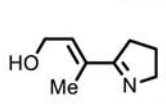
(7) Kozikowski, A.; Greco, M. N. *J. Org. Chem.* **1984**, *49*, 2310–2314.

(8) (a) Chida, N. Keio University, personal communication, 2008. Recently, Feldman et al. have developed allenyl azide cycloaddition chemistry which produces bicyclic unsaturated imines. See: (b) Feldman, K. S.; Antoline, J. F. *Org. Lett.* **2012**, *14*, 934–937. (c) Feldman, K. S.; Iyer, M. R. *J. Am. Chem. Soc.* **2006**, *127*, 4590–4591.

(9) Eckert, F.; Leito, I.; Kaljurand, I.; Kütt, A.; Klamt, A.; Diedenhofen, M. *J. Comput. Chem.* **2009**, *30*, 799–810.

Table 2. Scope of the Reaction



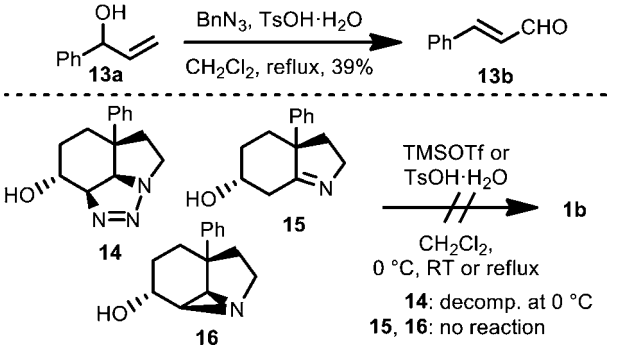
entry	substrates		products		yield (%)[b]
					
1	R = H	**2aa**		**2b**	83
2	R = MOM	**2ab**			76
3	R = TBS	**2ac**			73
4	R = Me	**2ad**			56
5	R = Ac	**2ae**			65
					
6	R = H	**3aa**		**3b**	61
7	R = MOM	**3ab**			61
8		**4**			63
9		**5**			35[c]
10		**6**		**1b**	83
11		**7a**		**7b**	n.r.
12		**8a**		**8b**	n.r.
13		**9a**		**9b**	0
14[d]		**10a**		**10b**	61
15		**11a**		**11b**	60
16[d]		**12a**[e]		**12b**	37

[a] Except for entries 14 and 16. [b] Isolation yield. [c] Lack of reproducibility. [d] Reaction conditions: TFA (5 equiv), CH_2Cl_2, −50 °C, 10 min (entry 14); $TsOH \cdot H_2O$, CH_2Cl_2, reflux, 20 min (entry 16). [e] E/Z = 3/20. n.r. = no reaction.

higher temperatures, much longer reaction times, and strong acid conditions (TfOH in most case, pK_a = 2.4 in CH_3CN).[5] Thus, utilizing allylic alcohols as a carbocation source is highly advantageous.

To improve the reaction conditions, the reaction temperature was cooled down to room temperature, but an excess amount of acid was necessary for full conversion of **1a** in 1 h (entry 3).[10] Because TsOH was not well soluble at room temperature (entry 4), a liquid methanesulfonic acid (pK_a = 9.97 in CH_3CN) was used and could provide **1b** in 58% yield in a 40 min reaction at 0 °C (entry 5). Finally, trimethylsilyl trifluoromethanesulfonate (TMSOTf) was found to be the best to carry out the reaction at 0 °C in good yield (entry 6). With TMSOTf, the reaction was accomplished in only 10 min.[11] An additive-free reaction (entry 7), other aprotic/protic solvents, or basic conditions (not shown) did not afford the desired products. Additionally, the introduction of leaving groups such as Ts, Ms, and Tf or halogens on **1a** for an S_N2' type Schmidt reaction under basic conditions destroyed the starting material, and our desired α,β-unsaturated imines were not observed.[5i,12]

Scheme 2



With optimal conditions determined, our focus was directed toward the substrate study and the reaction mechanism of this transformation (Table 2). Acyclic compound **2aa** was delivered to **2b** in good yield (entry 1). Not only a protecting-group-free hydroxy group but also OH-protected **2ab**−**ae** could afford **2b** in good yield (entries 2−5). From both (*E*)-olefin **3aa**, **3ab** and (*Z*)-olefin **4**, *trans*-conjugated imine **3b** was obtained in a similar yield regardless of the protection (entries 6−8). Interestingly, the importance of the position of the hydroxy group was revealed by substrate **5**, which could give the same product **3b** from **3aa** but in a much lower yield than those of entries 6−8 and without reproducibility (entry 9). Probably, an association of the S_N2 reaction might have an effect in this case.[5i] Compared to entry 6 in Table 1, **6**, an epimer of **1a**, could also give **1b** in a similar yield (entry 10). In contrast, **7a**,

(10) Reaction with 1.2 equiv of TFA gave recovered starting material.

(11) $BF_3 \cdot OEt_2$ also worked enough, but in a slightly lower yield (74%).

(12) Only in mesylation, a trace amount of unsaturated imine was observed by using an excess of reagents (triethylamine, MsCl). But it seemed to be generated by an acidic ammonium mesylate salt.

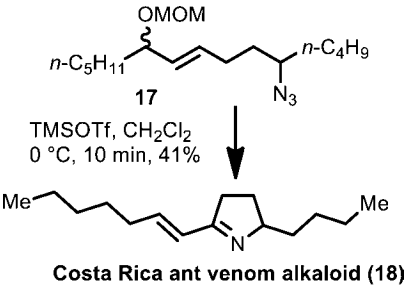
a deoxy compound of **1a**, did not give any products, but rather the recovered **7a** (entry 11).[13] The reaction with primary alcohol **8a** or **9a** did not afford unsaturated imine **8b** or **9b** (entries 12–13, **8a**: recovered, **9a**: decomposed). With tertiary alcohol **10a** (entry 14), conversion to **10b** was achieved with the weaker acid TFA at the lower temperature −50 °C. With trisubstituted olefins, not only alcohol **11a** but also epoxide **12a** could be transformed to **11b** and **12b** in moderate yields (entries 15–16). Due to the instability of **12a**–**b** (entry 16), TsOH gave a better result than that with TMSOTf (28% at 0 °C).

We also investigated intermolecular reactions (Scheme 2),[14] and cinnamaldehyde **13b**, a hydrolysis product of the resulting aldimine, was generated from **13a** in 39% yield. No ketone or ketimine was observed.[5h,15]

To exclude reaction pathways,[5h,i,6f] we submitted three possible intermediate compounds **14**–**16**,[16] but none of the three were converted to **1b**. Considering these facts along with the results of Table 2 (no [3 + 3] or [3 + 2] products were observed),[5h] our reaction suggests a carbocation-mediated S_N2'-type Schmidt reaction (Scheme 1b).[17]

With this established method, we demonstrated a total synthesis of a conjugated pyrroline alkaloid from the venom of the Costa Rican ant *Megalomyrmex foreli*.[18] The MOM-masked cyclization precursor **17** prepared from valeraldehyde[19] was treated with TMSOTf at 0 °C for 10 min, and the desired acid-labile cyclic unsaturated iminium alkaloid **18** was synthesized without a deprotection step (Scheme 3).[20]

Scheme 3. Synthesis of Ant Venom Alkaloid



In conclusion, we have demonstrated an efficient intramolecular transformation from substrates possessing azides and allylic secondary/tertiary alcohols to α,β-unsaturated alkylimines. Most reactions were performed with TMSOTf at 0 °C and were accomplished in 10 min. Allyl alcohols and allyl epoxides of cyclic and acyclic compounds were acceptable, and the use of readily accessible functional groups gave us a wide extension of acceptable substrates and improved reaction conditions to perform rapid transformation and afford α,β-unsaturated imines at low temperatures. The efficiency of this synthetic strategy was demonstrated by the total synthesis of an ant venom alkaloid. Further investigation of reaction mechanisms and applications toward concise alkaloid synthesis is currently underway.

Acknowledgment. This work was partly supported by funding from NAIST for young scientists working on photonanoscience. We are grateful to Prof. Noritaka Chida of Keio University for fruitful discussions and suggestions. We also thank Ms. Mika Yamamura, Ms. Yuriko Nishiyama, Ms. Yoshiko Nishikawa (HRMS measurement), and Mr. Shohei Katao (X-ray crystallographic analysis) of NAIST.

Supporting Information Available. Reaction procedures, preparations, and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) A thermal transformation of **7a** into **7b** via [3 + 2] cyclization was successful (toluene, reflux, 3h, 86%). See Supporting Information.

(14) (a) Barbero, M.; Cadamuro, S.; Dughera, S.; Venturello, P. *Synthesis* **2008**, 1379–1388. For a detailed mechanistic study, see: (b) Jia, A. K.; Ottosson, H.; Zen, X.; Thibblin, A. *J. Org. Chem.* **2002**, *67*, 182–187. (c) Goering, H. L.; Dilgren, R. E. *J. Am. Chem. Soc.* **1959**, *81*, 2556–2561. (d) The reaction with *trans*-cinnamyl alcohol gave **14b** in 20% yield without ketones or ketimines.

(15) We confirmed that **14b** and a promising unsaturated ketone product were tolerable enough under the reaction conditions and that **14b** was not produced in the absence of benzyl azide.

(16) Deposited crystallographic data for the bromobenzoate of **14**, **16** and a synthetic intermediate of **1a** with the Cambridge Crystallographic Data Center are the following: CCDC 869959, 869960, and 869961.

(17) A cation-trapping experiment with **2aa** also gave only **2b**.

(18) Jones, T. H.; DeVries, P. J.; Escoubas, P. *J. Chem. Ecol.* **1991**, *17*, 2507–2518. The absolute stereochemistry or optical rotation value was not provided in this paper.

(19) See Supporting Information.

(20) Alkaloid **18** was slightly sensitive to silica gel, and its volume was halved after passing through silica gel. Use of triethylamine-containing elution or alumina was not effective for purification.