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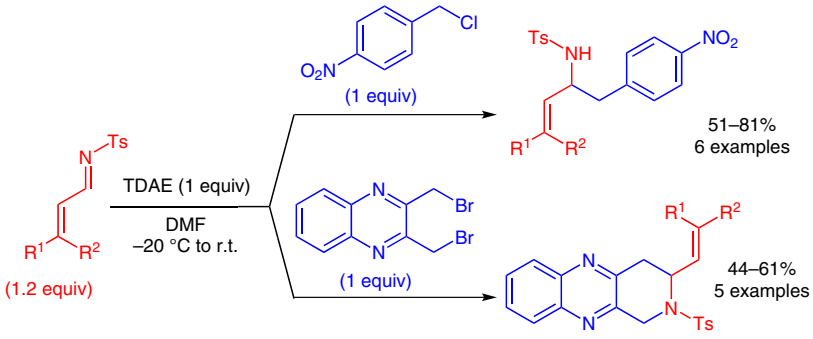
Cédric Spitz
Thierry Terme
Patrice Vanelle*

Aix-Marseille Université, CNRS, ICR UMR 7273, Equipe Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, 27 Boulevard Jean Moulin – CS 30064 – 13385 Marseille Cedex 05, France
patrice.vanelle@univ-amu.fr



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Abstract A mild and metal-free regioselective 1,2-addition of carbon nucleophiles to α,β-unsaturated imines has been developed. Good yields and total regioselectivities were achieved by addition of *p*-nitrobenzyl chloride or 2,3-bis(bromomethyl)quinoxaline to α,β-unsaturated tosylimines.

Key words α,β-unsaturated tosylimines, regioselectivity, TDAE, addition, metal-free

Allylic amines represent an important structural motif in organic synthesis because of their high versatility in a wide range of organic transformations including asymmetric total syntheses.[1] Furthermore, allylic amine functionality is found in biologically active compounds.[2] Of the different methods available to construct the allylamine scaffold, adding organometallic reagents to α,β-unsaturated imines is one of the most commonly used. When a nucleophile is added to α,β-unsaturated tosylimines, it can lead to 1,2-addition or 1,4-addition. This is influenced by several factors, such as the nature of both organometallic species and substrates. As a general rule, organolithiums are by far the most popular reagents to promote 1,2-addition, whereas organocuprates predominantly promote conjugate addition.

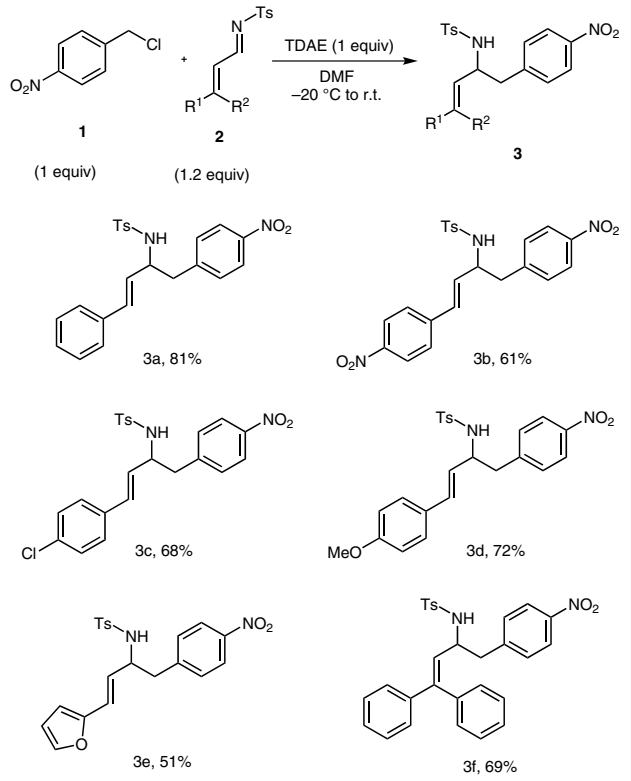
Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent, that reacts with halogenated derivatives to generate a carbanion under mild conditions.[3] In particular, we have shown that from *o*- and *p*-nitrobenzyl chlorides, TDAE is able to generate a nitrobenzyl carbanion that can react with various electrophiles such as aromatic aldehydes, α-ketoester, ketomalonate, α-ketolactam, and imine derivatives.[4]

In this study we wished to determine how the carbanion generated by our metal-free conditions would react in the presence of α,β-unsaturated imines. As part of our research program to develop new bioactive compounds,[5] we report herein the application of our TDAE methodology for the regioselective 1,2-addition of *p*-nitrobenzyl chloride (**1**) or 2,3-bis(bromomethyl)quinoxaline (**4**) to a variety of α,β-unsaturated tosylimines **2**.

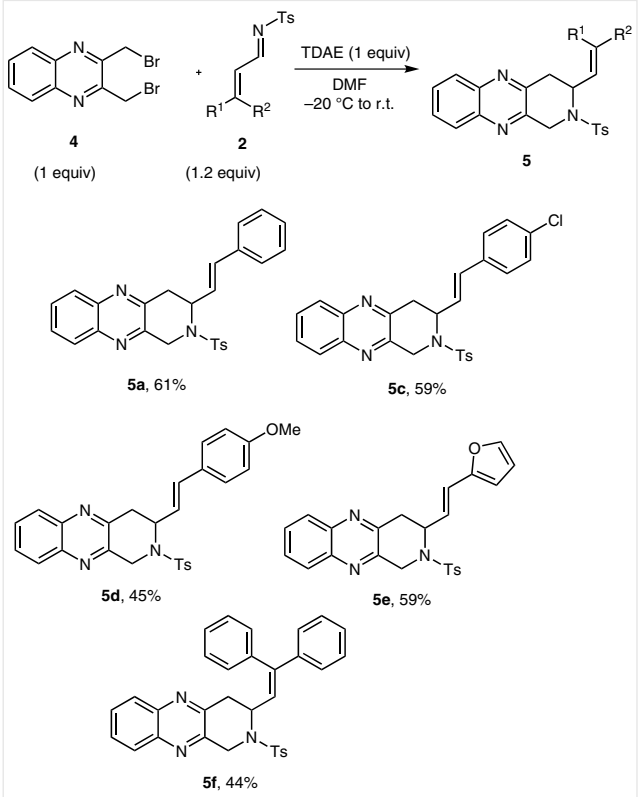
The reaction between *p*-nitrobenzyl chloride (**1**) and various α,β-unsaturated *N*-tosylimines **2a–f** in the presence of TDAE at –20 °C for one hour, followed by two hours at room temperature, led to the corresponding allylamines[6] in good yields (51–81%) and with total 1,2-regioselectivity (Scheme 1). Reactions with both electron-poor and electron-rich imines produced good yields and complete regioselectivities. Interestingly, the heteroaromatic imine **2e** allowed the formation of the corresponding amine **3e** in good yield. Moreover, the more bulky β-disubstituted imine **2f** gave only the product of 1,2-addition **3f** in 69% yield.

The structure of amine **3a**, the only regioisomer formed by reaction of *p*-nitrobenzyl chloride (**1**) with imine **2a**, was determined by X-ray crystal structure analysis (Figure 1).[7]

Figure 1 X-ray crystal structure of **3a**



Scheme 1 Regioselective 1,2-addition of *p*-nitrobenzyl chloride (**1**) to α,β-unsaturated tosylimines **2** using the TDAE strategy. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.24 mmol), and TDAE (0.2 mmol) in anhydrous DMF stirred at –20 °C for 1 h and then maintained at r.t. for 2 h; yields are isolated yields after purification by chromatography.



Scheme 2 Regioselective 1,2-addition of 2,3-bis(bromomethyl)quinoxaline (**4**) to α,β-unsaturated tosylimines **2** using the TDAE strategy. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.24 mmol), and TDAE (0.2 mmol) in anhydrous DMF stirred at –20 °C for 1 h and then maintained at r.t. for 2 h; yields are isolated yields after purification by chromatography.

Since 2003, we have introduced a new program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry.[8] In this context, we recently described the synthesis of quinoxaline derivatives which could offer very interesting biological properties.[9] Thus, we describe herein the metal-free synthesis of five new substituted pyrido[3,4-*b*]quinoxalines using TDAE in the presence of 2,3-bis(bromomethyl)quinoxaline (**4**) and various α,β-unsaturated *N*-tosylimines **2** (Scheme 2).

Both electron-poor and electron-rich imines produced good yields and complete regioselectivities. Interestingly, the reaction conditions are tolerant with the formation of amine **5e** from heteroaromatic imine **2e**. Moreover, the more bulky β-disubstituted imine **2f** gave only the product of 1,2-addition **5f** in 44% yield. The mechanism could involve nucleophilic addition of carbanion formed by the action of TDAE with 2,3-bis(bromomethyl)quinoxaline on the imine group of sulfonimine **2** followed by an intramolecular nucleophilic substitution of the second bromomethyl group.[9b]

In conclusion, the regioselective addition of *p*-nitrobenzyl chloride (**1**) or 2,3-bis(bromomethyl)quinoxaline (**4**) to α,β-unsaturated tosylimines using the TDAE strategy allowed the synthesis of allylamines in good yields and complete 1,2-regioselectivity. The tolerance of nitro groups and heteroaromatic nucleophiles such as quinoxaline derivatives suggests that this method is a good alternative to the use of organometallic reagents to prepare allylic amines. Further research is in progress to extend the scope to an asymmetric version using enantiopure α,β-unsaturated *N*-sulfinimines.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560574.

References and Notes

(1) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.
(2) (a) Petranyi, G.; Ryder, N. S.; Stutz, A. *Science* **1984**, 1239. (b) Ghannoum, M.; Isham, N.; Verma, A.; Plaum, S.; Fleischer, A. Jr.; Hardas, B. *Antimicrob. Agents Chemother.* **2013**, 4369. (c) Marín, M. T.; Margarit, M. V.; Salcedo, G. E. *Farmaco* **2002**, *57*, 723.
(3) (a) Takechi, N.; Aït-Mohand, S.; Médebielle, M.; Dolbier, W. R. Jr. *Tetrahedron Lett.* **2002**, *43*, 4317. (b) Pooput, C.; Médebielle, M.; Dolbier, W. R. Jr. *Org. Lett.* **2004**, *6*, 301. (c) Pooput, C.; Médebielle, M.; Dolbier, W. R. Jr. *J. Org. Chem.* **2006**, *71*, 3564.
(4) (a) Giuglio-Tonolo, G.; Terme, T.; Médebielle, M.; Vanelle, P. *Tetrahedron Lett.* **2003**, *44*, 6433. (b) Giuglio-Tonolo, G.; Terme, T.; Médebielle, M.; Vanelle, P. *Tetrahedron Lett.* **2004**, *45*, 5121. (c) Khoumeri, O.; Terme, T.; Vanelle, P. *Synthesis* **2009**, 3677. (d) Khoumeri, O.; Giuglio-Tonolo, G.; Crozet, M. D.; Terme, T. M.; Vanelle, P. *Tetrahedron* **2011**, *67*, 6173. (e) Spitz, C.; Khoumeri, O.; Terme, T.; Vanelle, P. *Synlett* **2013**, *24*, 1725. (f) Broggi, J.; Terme, T.; Vanelle, P. *Angew. Chem. Int. Ed.* **2014**, *53*, 384.
(5) (a) Vanelle, P.; Maldonado, J.; Madadi, N.; Gueiffier, A.; Teulade, J.-C.; Chapat, J.-P.; Crozet, M. P. *Tetrahedron Lett.* **1990**, *31*, 3013. (b) Delmas, F.; Gasquet, M.; Timon-David, P.; Madadi, N.; Vanelle, P.; Vaille, A.; Maldonado, J. *Eur. J. Med. Chem.* **1993**, *28*, 23. (c) Crozet, M. D.; Botta, C.; Gasquet, M.; Curti, C.; Remusat, V.; Hutter, S.; Chapelle, O.; Azas, N.; De Méo, M.; Vanelle, P. *Eur. J. Med. Chem.* **2009**, *44*, 653. (d) Dunn, L. A.; Burgess, A. G.; Krauer, K. G.; Eckmann, L.; Vanelle, P.; Crozet, M. D.; Gillin, F. D.; Upcroft, P.; Upcroft, J. A. *Int. J. Antimicrob. Agents* **2010**, *36*, 37. (e) Kieffer, C.; Cohen, A.; Verhaeghe, P.; Hutter, S.; Castera-Ducros, C.; Laget, M.; Remusat, V.; M'Rabet, M. K.; Rault, S.; Rathelot, P.; Azas, N.; Vanelle, P. *Eur. J. Med. Chem.* **2015**, *92*, 282.
(6) **General Procedure**
To a stirred solution of *p*-nitrobenzyl chloride (**1**) or 2,3-bis(bromomethyl)quinoxaline (**4**, 0.2 mmol) and *N*-tosylimine **2** (0.24 mmol) in DMF (1 mL) at –20 °C was added TDAE (0.2 mmol). The solution was vigorously stirred at –20 °C for 1 h and then maintained at r.t. for 2 h. Water (5 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with H_2O (20 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent furnished the crude product. Purification by silica gel chromatography (PE–EtOAc from 8:2 to 7:3 depending on the polarity of substrate) afforded pure amine products **3** or **5**.
(*E*)-4-Methyl-*N*-(1-(4-nitrophenyl)-4-phenylbut-3-en-2-yl)benzenesulfonamide (3a)
81% yield; yellow solid; mp 189–191 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 2 H), 7.60 (d, *J* = 8.1 Hz, 2 H), 7.26–7.12 (m, 9 H), 6.24 (d, *J* = 15.9 Hz, 1 H), 5.85 (dd, *J* = 15.9, 7.0 Hz, 1 H), 4.75 (d, *J* = 7.9 Hz, 1 H), 4.29–4.18 (m, 1 H), 3.03–2.98 (m, 2 H), 2.31 (s, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 147.0, 144.4, 143.8, 137.6, 135.8, 132.5, 130.5, 129.7, 128.7, 128.3, 127.4, 127.2, 126.6, 123.8, 56.9, 42.3, 21.5. ESI-HRMS: *m/z* $[M + NH_4]^+$ calcd for $[C_{23}H_{26}N_3O_4S]^+$: 440.1639; found: 440.1640.
(*E*)-3-Styryl-2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline (5a)
61% yield; yellow solid; mp 72–75 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.02–7.95 (m, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H), 7.75–7.71 (m, 2 H), 7.22–7.16 (m, 5 H), 7.05–7.01 (m, 2 H), 6.38 (d, *J* = 16.1 Hz, 1 H), 5.86 (dd, *J* = 16.1, 5.5 Hz, 1 H), 5.32 (br s, 1 H), 5.12 (d, *J* = 17.6 Hz, 1 H), 4.50 (d, *J* = 17.6 Hz, 1 H), 3.55 (dd, *J* = 17.3, 5.9 Hz, 1 H), 3.38 (dd, *J* = 17.3, 2.0 Hz, 1 H), 2.34 (s, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 149.4, 148.0, 144.1, 141.9, 141.4, 136.3, 135.7, 134.2, 130.1, 130.0, 128.8, 128.7, 128.6, 128.3, 127.7, 126.6, 124.6, 53.4, 46.4, 36.9, 21.6 (one carbon missing due to overlap). ESI-HRMS: *m/z* $[M + H]^+$ calcd for $[C_{26}H_{24}N_3O_2S]^+$: 442.1584; found: 442.1584.
(7) CCDC 1413021 contains the supplementary crystallographic data of compound **3a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
(8) (a) Montana, M.; Terme, T.; Vanelle, P. *Tetrahedron Lett.* **2006**, *47*, 6573. (b) Montana, M.; Crozet, M. D.; Castera-Ducros, C.; Terme, T.; Vanelle, P. *Heterocycles* **2008**, *75*, 925. (c) Since, M.; Terme, T.; Vanelle, P. *Tetrahedron* **2009**, *65*, 6128. (d) Juspin, T.; Terme, T.; Vanelle, P. *Synlett* **2009**, 1485. (e) Juspin, T.; Giuglio-Tonolo, G.; Terme, T.; Vanelle, P. *Synthesis* **2010**, 844.
(9) (a) Montana, M.; Terme, T.; Vanelle, P. *Tetrahedron Lett.* **2005**, *46*, 8373. (b) Khoumeri, O.; Terme, T.; Vanelle, P. *Tetrahedron Lett.* **2012**, *53*, 2410.