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Direct Amination of Olefins through Sequential Triazolinedione Ene Reaction and Carbanion-Assisted Cleavage of the N–N Urazole Bond

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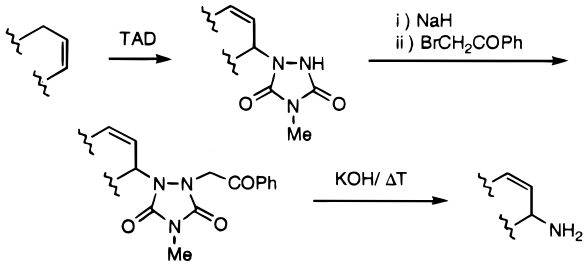
ABSTRACT



Allylic amines 5 are obtained in 30–55% overall yields by the base-catalyzed hydrolysis of trialkylated allylic urazoles 3; the latter are prepared by the TAD ene reaction of the appropriate olefin and further N-alkylation with α-bromoacetophenone. The proposed mechanism for this novel urazole rupture is based on the generation of a carbanion adjacent to the hydrazide functionality, which induces urazole ring-opening by cleavage of the N–N bond.

Allylic amines are versatile and valuable building blocks in organic synthesis, for which efficient and convenient methods of preparation are still in great demand.[1] Besides nucleophilic substitution, the direct electrophilic allylic amination of alkenes constitutes a useful and attractive methodology, since allylic functionalization is accomplished readily through a single-step process. The aza ene reaction deserves special consideration, since an azo enophile directly transforms olefins to allylic hydrazides ("masked" allylic amines).[2,3] However, despite the promising opportunities of the aza ene reaction for direct allylic amination, such an approach has been exploited to a limited extent.[3a,4] The major problem resides in the need for an expedient hydrolysis of the resulting hydrazide and a selective cleavage of the N−N bond in the corresponding hydrazine to set free the desired allylic amine.

Another issue is the reactivity of the azo enophile. Acyclic azodicarboxylates are quite sluggish enophiles and are, thus, of limited applicability especially for electron-poor olefinic substrates. In contrast, the cyclic 1,2,4-triazoline-3,5-diones[5]

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(1) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708.
(2) Moody, C. J. *Adv. Heterocycl. Chem.* **1982**, *30*, 1−45.
(3) (a) Brimble, M. A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5261−5263. (b) Davies, A. G.; Kinart, W. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2281−2284. (c) Kinart, W. J. *J. Chem. Res., Synop.* **1994**, 486-487.
(4) Leblanc, Y.; Zamboni, R.; Bernstein, M. A. *J. Org. Chem.* **1991**, *56*, 1971−1972.
(5) Rádl, S. *Adv. Heterocycl. Chem.* **1996**, *67*, 119−205.
(6) (a) Elemes, Y.; Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1989**, *30*, 6903−6906. (b) Orfanopoulos, M.; Elemes, Y.; Stratakis, M. *Tetrahedron Lett.* **1990**, *31*, 5775−5778. (c) Elemes, Y.; Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1997**, *38*, 6437−6440.
(7) (a) Adam, W.; Wirth, T.; Pastor, A.; Peters, K. *Eur. J. Org. Chem.* **1998**, 501−506. (b) Stratakis, M.; Vassilikogiannakis, G.; Orfanopoulos, M. *Tetrahedron Lett.* **1998**, *39*, 2393−2396. (c) Adam, W.; Nestler, B.; Pastor, A.; Wirth, T. *Tetrahedron Lett.* **1998**, *39*, 2625−2628. (d) Gau, A.-H.; Lin, G.-L.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *J. Org. Chem.* **1999**, *64*, 2194−2201. (e) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M.; Foote, C. S. *J. Org. Chem.* **1999**, *64*, 4130−4139.

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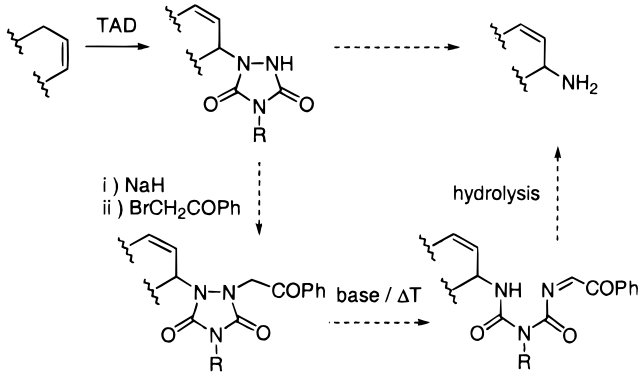
(TAD) are excellent enophiles (nearly quantitative yields and high regio-[6] and diastereoselectivities[7]), but the resulting urazoles are extremely resistant to hydrolysis compared to the hydrazides from the azodicarboxylates.[8] Even if an adequate method for the hydrolysis of ene-derived urazole were available, the selective cleavage of the N−N bond in the hydrazine, i.e., under preservation of the allylic double bond, is difficult. The only work along these lines dates back over 25 years, when Corey and Snider transformed an ene-derived urazole to the corresponding amine; however, the allylic double bond had to be sacrificed by dihydroxylation, although the latter oxyfunctionalization was their synthetic goal.[9]

Scheme 1



A careful literature survey of the urazole chemistry reveals sporadic reports that the N−N bond in the 1,2,4,-triazolidine ring may be directly severed without the need of hydrolytic action. Besides the specialized photochemical transformations of this type,[10] a potentially valuable process for synthetic purposes corresponds to the carbanion-assisted NN-bond cleavage.[11] We report herein the first synthesis of allylic amines from ene-type urazoles. This new method is displayed in Scheme 1 and is based on the novel concept of carbanion-assisted cleavage of the N−N bond in the urazole ring. The main advantage of the present methodology is not only the utilization of TAD as one of the best enophiles (high reactivity, regio- and diastereoselectivity) but that the amine is directly released from the urazole without the need of a reductive step for the N−N bond cleavage.

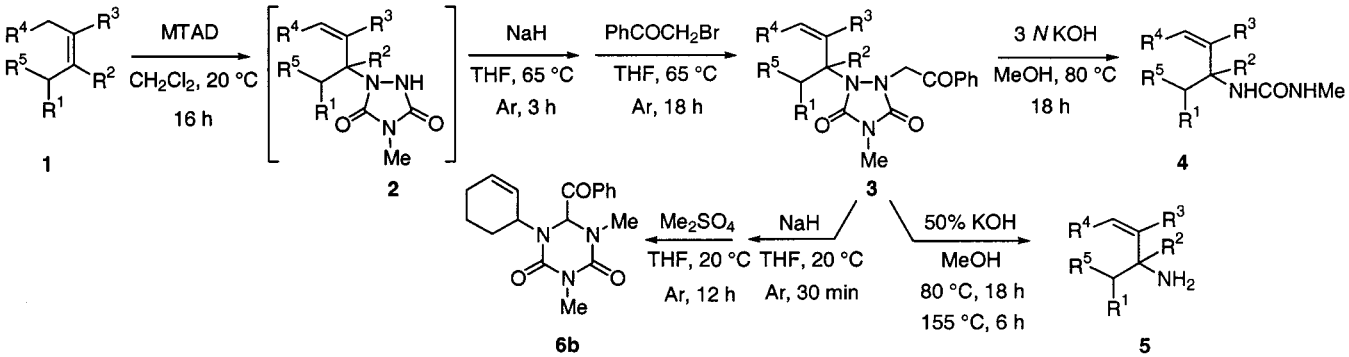
The ene reaction of the alkenes **1a**−**f** with MTAD (4-methyl-1,2,4-triazoline-3,5-dione) afforded under standard conditions[12] the corresponding allylic urazoles **2a**−**e** and *threo*-**2′f** quantitatively. These were used in the next step without further purification (Scheme 2).

For the methyl derivative of mesitylol **1e,** the ene reaction with MTAD led expectedly in a low diastereoselectivity[7b−e] to a 54:46 mixture of threo/erythro diastereomers of **2e**.

In contrast, the ene reaction of mesitylol (**1f**) itself with MTAD displayed good diastereoselectivity (dr 87:13), a consequence of the well-established directing effect of the hydroxy group,[7b−e] to give *threo*-**2′f** as the major diastereomer. The diastereomeric mixture was enriched in the *threo*-**2′f** urazole (up to dr 95:5) by recrystallization. For all subsequent transformations, the hydroxy group was protected in the form of its tetrahydropyran derivative[13] to afford the urazole *threo*-**2f** in 67% yield (cf. Supporting Information).

N-Alkylation of the urazoles **2a**−**e** and *threo*-**2f** was conducted in THF, by sequential deprotonation with 1 equiv of sodium hydride and treatment with α-bromoacetophenone, to give the allylic urazoles **3a**−**e** and *threo*-**3f** in 44−81%

Scheme 2

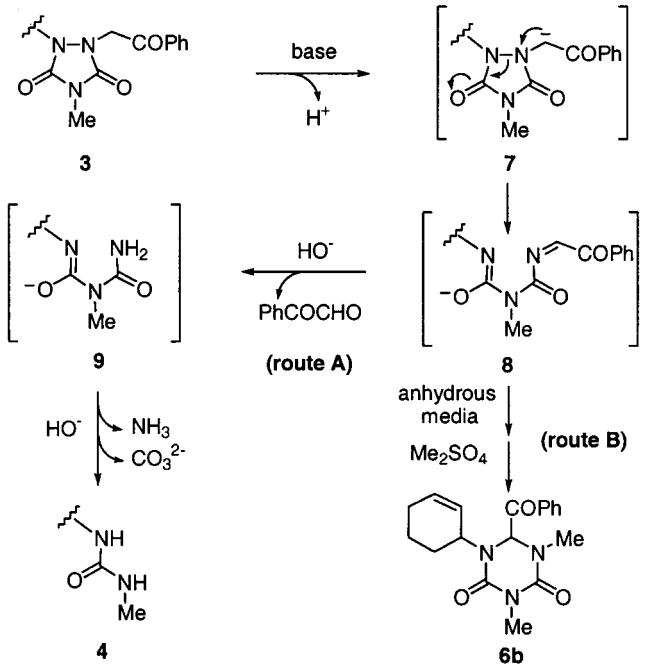


entry	compound	R^1	R^2	R^3	R^4	R^5	**3** (%)	**4** (%)[a]	**5** (%)[a]
1	**a**	H	H	H	-CH_2-		78	58	45 [b]
2	**b**	H	H	H	-$(CH_2)_2$-		81	72	67
3	**c**	H	H	H	-$(CH_2)_3$-		70	68	68
4	**d**	H	Me	Me	H	H	60	62	40 [b]
5	**e**	OMe	H	Me	H	Me	44 [c]	64 [c]	45 [b,c]
6	***threo*-f**	OH[d]	H	Me	H	Me	78 [e]	70 [e]	41 [e]

[a] Calculated based on **3**; [b] ethylene glycol instead of MeOH was used as solvent, *cf. Supporting Information*; [c] isolated as a *threo/erythro* mixture of diastereomers (d.r. 52:48, determined from the areas of characteristic peaks in the ^{1}H NMR spectrum), error ± 5 of the stated value; [d] the ene reaction was conducted on the mesitylol directly, for all subsequent steps the OH group was protected in terms of the tetrahydropyran derivative (cf. Supporting Information); [e] isolated as one diastereoisomer (d.r. > 95:5, cf. footnote *c*)

yield (Scheme 2). The cleavage of the urazoles **3** was performed by treatment with 3 N potassium hydroxide in methanol at 80 °C. Under these conditions, the allylic ureas **4a**−**e** and *threo*-**4f** were isolated in 58−72% yield. This unusual transformation may be rationalized in terms of proton abstraction at the methylene group in urazole **3** to give carbanion **7** (Scheme 3). The ring opening of **7** to **8** is favored

Scheme 3



by the good leaving-group ability of the ureido fragment. The latter is hydrolyzed under the reaction conditions, first to a deprotonated biuret intermediate **9** and subsequently to the urea **4** (Scheme 3; route A). The allylic amines **5a**−**e** and *threo*-**5f** were released from the in-situ-generated allylic ureas **4** by hydrolysis with 50% solution of aqueous KOH; first the mixture was heated at 80 °C and then at 155 °C in a sealed tube for 6 h. The free amines were isolated as the only products in 40−68% yield (Scheme 2).

This unprecedented methodology constitutes a significant improvement since for the first time allylic amines may be obtained from the corresponding TAD ene adducts in up to 55% overall yields. *Although this procedure entails a multistep sequence, only the trialkylated urazoles **3** need to be isolated; the remaining steps are conducted in a one-pot process!*

The treatment of the urazole **3b** with 1 equiv of sodium hydride under anhydrous conditions, followed by addition of dimethyl sulfate, led to the 1,3,5-triazine-2,4-dione **6b** in 80% yield (Scheme 2). Since only 1 equiv of base was employed under anhydrous conditions, the acylimino intermediate **8** does not afford the corresponding biuret derivative **9** (Scheme 3), but instead, intramolecular nucleophilic attack is preferred to result in a six-membered ring of the anionic 1,3,5-triazinedione intermediate (not shown). Treatment with dimethyl sulfate and in situ methylation at the amidate nitrogen site afforded finally the triazinedione **6b** (Scheme 3; route B).

In conclusion, a new and effective tandem process, namely TAD ene reaction followed by the novel carbanion-assisted cleavage of the N−N urazole bond, has been developed for the direct allylic amination of simple and functionalized olefins. This method employs a one-pot, multistep procedure in which only the trialkylated urazoles **3** need to be isolated. Most significant, the diastereoselective and regioselective TAD ene reaction with chiral allylic alcohols, i.e., mesitylol (**1f**), permits the preparation of the functionalized threo-configured allylic amine derivative *threo*-**5f**.

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Supporting Information Available: Complete experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Corey, E. J.; Snider, B. B. *J. Org. Chem.* **1973**, *38*, 3632−3633. (b) Adam, W.; Arias, L. A.; De Lucchi, O. *Synthesis* **1981**, 543−545. (c) Meehan, S.; Little, R. D. *J. Org. Chem.* **1997**, *62*, 3779−3781.

(9) Corey, E. J.; Snider, B. B. *Tetrahedron Lett.* **1973**, 3091−3094.

(10) (a) Sheradsky, T.; Moshenberg, R. *J. Org. Chem.* **1984**, *49*, 587−590. (b) Tanaka, S.; Seguchi, K.; Itoh, K.; Sera, A. *Chem. Lett.* **1994**, 771−774. (c) Tanaka, S.; Seguchi, K.; Itoh, K.; Sera, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3533−3542.

(11) (a) Wamhoff, H.; Wald, K. *Chem. Ber.* **1977**, *110*, 1716−1729. (b) Adam, W.; Grabowski, S.; Hinz, R. F.; Lucchini, V.; Peters, E.-M.; Peters, K.; Rebollo, H.; Schnering, H. G. *Chem. Ber.* **1987**, *120*, 2075−2079. (c) Atkinson, R. S.; Edwards, P. J.; Thomson, G. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3209−3216.

(12) (a) Ohashi, S.; Leong, K.; Matyjaszewski, K.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3467−3471. (b) Ohashi, S.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3472−3476.

(13) Fichert, T.; Massing, U. *Tetrahedron Lett.* **1998**, *39*, 5017−5018.