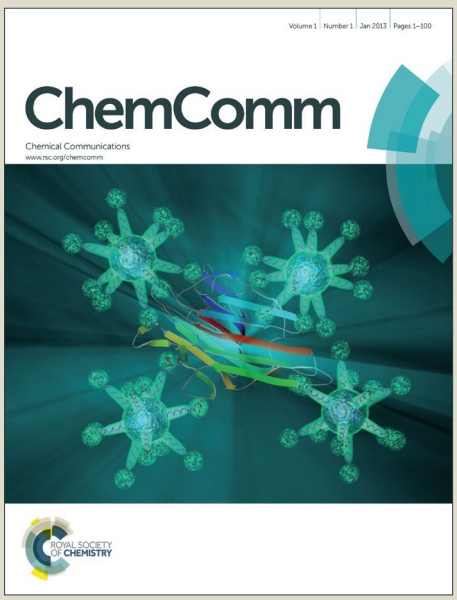
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

Diastereoselective Synthesis of Substituted Diaziridines from Simple Ketones and Aldehydes

Cite this: DOI: 10.1039/x0xx00000x

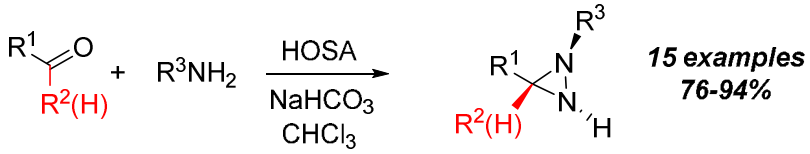
Alexander W. Beebe,[§] Emma F. Dohmeier,[†] and Gustavo Moura-Letts*[§]

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/chemcomm

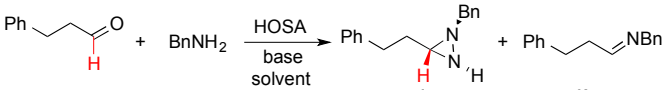
Diastereopure substituted diaziridines from simple aldehydes; ketones and amines are here reported. These important chemical scaffolds are obtained in the presence of a weak inorganic base and hydroxylamine *O*-sulfonic acid (HOSA). This method introduces three stereocenters in one step to provide a wide variety of substituted diaziridines with high yields and diastereoselectivities.



The design and preparation of efficient methods for the synthesis of *N*-containing heterocycles remains a cornerstone in organic chemistry.[1] Small heterocycles have been a popular synthetic target since the birth of organic chemistry for the development of reagents, building blocks and pharmaceuticals.[2] On the other hand, diaziridines have been often prepared as precursors for other reactions.[3] *N*-monosubstituted diaziridines have been used as *N*-transfer reagents to α,β-unsaturated amides to selectively form stereopure aziridines.[4] Unprotected diaziridines can be easily oxidized to the respective diazirines and further utilized as dipole precursors for dipolar cycloadditions.[5] Moreover, diaziridinones can be used for the palladium-mediated amination and diamination of dienes and esters.[6]

Recently, *N*-protected diaziridines have been shown to undergo dipolar cycloadditions with various π-systems.[7] Furthermore, substituted diaziridines have received attention for their pharmacological properties. Spirodiaziridines have been shown to be glycosidase inhibitors, and they also have been shown to inhibit the *O*-demethylation activity of P450 2B6 in a mechanism-based approach.[8] Thus, there is pressing need for the development of systematic methods for the synthesis of these highly relevant scaffolds.

Methods for the synthesis of diaziridines were first discovered as early as 1950.[9] This seminal work provided an understanding of their hydrazine-aminal dual behaviour. Previous studies have shown that the reaction of substituted imines and *N*-nosyl hydroxylamine *O*-esters can provide the respective diaziridines in good yields but limited scope.[10]



Entry	Stoichiometry[a]	Solvent	Additive	Ratio **1a**/**1b**	Yield[b]
1	1:3:1	H_2O	none	10/1	62%
2	1:3:1	THF	none	5/1	35%
3	1:3:1	toluene	none	8/1	53%
4	1:3:1	CH_2Cl_2	none	15/1	80%
5	1:3:1	$CHCl_3$	none	>20/1	82%
6	1:2:1	$CHCl_3$	none	>20/1	75%
7	1:1:1	$CHCl_3$	none	1/1	48%
8	1:1:1	$CHCl_3$	$NaHCO_3$	>20/1	88%
9	1:1:1	$CHCl_3$	K_3PO_4	>20/1	71%
10	1:1:1	$CHCl_3$	Et_3N	>20/1	64%

a. Aldehyde:Amine:HOSA. *b.*Isolated yields.

Table 1. Reaction discovery and optimization.

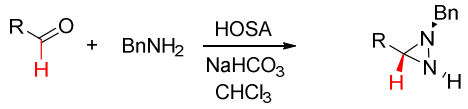
Recently an asymmetric version of the diaziridination of imines with *N*-benzyl hydroxylamine *O*-benzoyl esters was successfully developed.[11] This contribution relied on a cinchonine-derived chiral phase-transfer catalyst to achieve asymmetric induction. The scope, yields and enantioselectivities were limited to aromatic imines.

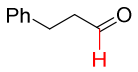
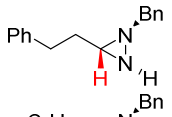
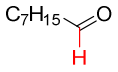
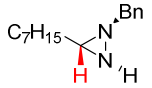
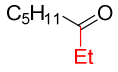
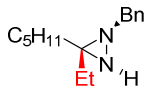
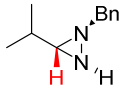
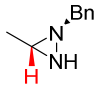
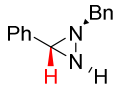
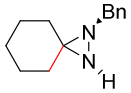
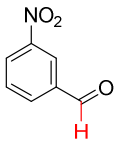
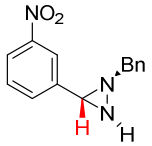
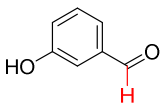
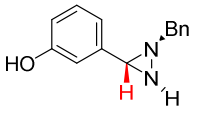
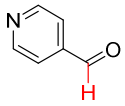
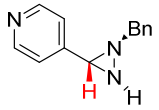
[§]*Department of Chemistry and Biochemistry, Rowan University, 201 Mullica Hill Rd, Glassboro, New Jersey, USA. E-mail:* ***moura-letts@rowan.edu***

[†]*Department of Chemical Engineering.*

Conversely, the diaziridination of aldehydes and amines in the presence of hydroxylamine *O*-sulfonic acid and esters as the source of *nitrogen* has also been reported.[12] However, these contributions are only limited to the diaziridination of cyclopentanone and benzylamine.

Thus, to the best our knowledge, there is a clear lack of a general method for the efficient synthesis of diaziridines starting from simple aldehydes, ketones and amines.



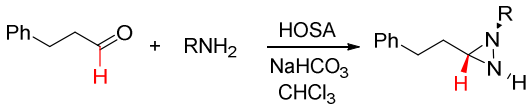
Entry	Aldehyde/Ketone	Diaziridine	Yield[a,b]
1			88%
2			89%
3			84%[c]
4			80%
5			85%
6			87%
7			91%
8			78%
9			80%
10			85%

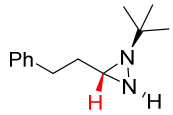
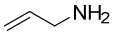
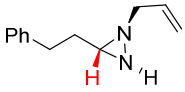
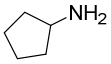
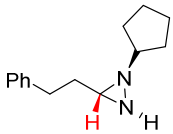
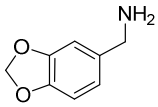
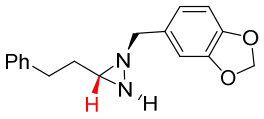
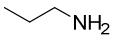
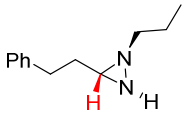
a. Isolated yields. *b*.Isolated as single diastereomers. *c*. Isolated as a 2:1 mixture of diastereomers.

Table 2. Reaction scope for aldehydes and ketones.

We started our study by assessing the diaziridination of benzyl amine and hydrocinnamaldehyde in the presence of HOSA. We screened a large array of solvents (**Table 1**), and we found that this reaction arrives to complete conversion in polar media, but yields are much higher when using $CHCl_3$ (Entry 5, 82% yield) compared to H_2O or THF (Entries 1 and 2, 62 and 35% yield respectively). Moreover, the ratio of diaziridine **1a** to imine **1b** increased from 10/1 to >20/1 when going from H_2O to $CHCl_3$. Other solvents like toluene (Entry 3, 53% yield) and CH_2Cl_2 (Entry 4, 80% yield) proved to be successful at providing the diaziridine product, but less efficient than the results obtained with $CHCl_3$.

We also sought to optimize the stoichiometry of the diaziridination. The diaziridination of cyclopentanone and benzylamine in the presence of HOSA is known to only provide good yields when a high excess (3 equiv.) of benzylamine is used. When we studied the effect of changing the stoichiometry, we found that the reaction provides the product with slightly lower yield with 2 equiv. of amine (Entry 6, 75% yield) and considerably lower yield and diaziridine/imine ratio with 1 equiv. (Entry 7, 48% yield, 1/1 ratio). However, upon replacing the excess amine with an inorganic base, the reaction productivity improved to 88% yield when using $NaHCO_3$ and 71% when using K_3PO_4. The reaction showed a lower yield when an organic base was used (Entry 10, Et_3N, 64% yield). Thus, the reaction appears to be optimal in a 1:1:1 stoichiometry with 1.5 equiv. of $NaHCO_3$ in $CHCl_3$.



Entry	Amine	Diaziridine	Yield[a]
1			89%
2			78%
3			76%
4			85%
5			94%

a.Isolated yields.

Table 3. Reaction scope for amines.

We then focused on assessing the scope of the reaction against a variety of aldehydes and ketones (**Table 2**). We found that alkyl aldehydes react with benzylamine and HOSA under the optimized conditions to provide the respective diaziridines in very good yields (Entries 1, 2, 4 and 5 in 88, 89, 80 and 85% yield respectively). Moreover, these diaziridines were obtained as single diastereomers.[13] We also wanted to study the diaziridination of alkyl ketones and we found that 3-octanone successfully provided the desired diaziridine in good yield (Entries 3, 84% yield) and as a 2:1 mixture of diastereomers. Similarly, cyclohexanone provided the expected diaziridine in high yields (Entry 7, 91% yield). Unfortunately, aromatic ketones failed to provide any diaziridination products under these conditions.[14]

We then focused on assessing the diaziridination of aromatic aldehydes. Benzaldehyde and *m*-nitrobenzaldehyde proved to work with good efficiencies and diastereoselectivities (Entries 6 and 8, 87

and 78% yield respectively). Moreover, we were surprised to find that 3-hydroxybenzaldehyde furnished the diaziridine product in good yield as well (Entry 9, 80%). We further extended the scope of this reaction to heterocyclic aromatic aldehydes and found that the respective heterocyclic diaziridine was obtained in high yield (Entry 10, 85%).

We also wanted to investigate the scope by changing the amine component of the reaction (**Table 3**). We initially tested the diaziridination of hydrocinnamaldehyde with alkyl amines (allyl and propyl amine), and we found that they also provide the diaziridine in good yields and as single diastereomers (Entries 2 and 5 with 78 and 94% respectively). Bulky alkyl amines like t-butyl and cyclopentyl amine were also successful at furnishing the desired diaziridines (Entries 1 and 3, 89 and 76% yield respectively). We were also interested in testing amines with pharmacophoric properties for the generation of a library for high-throughput-screening of their biological properties. Piperonylamine reacted to efficiently provide the respective diaziridine in high yield (Entry 4, 85% yield).

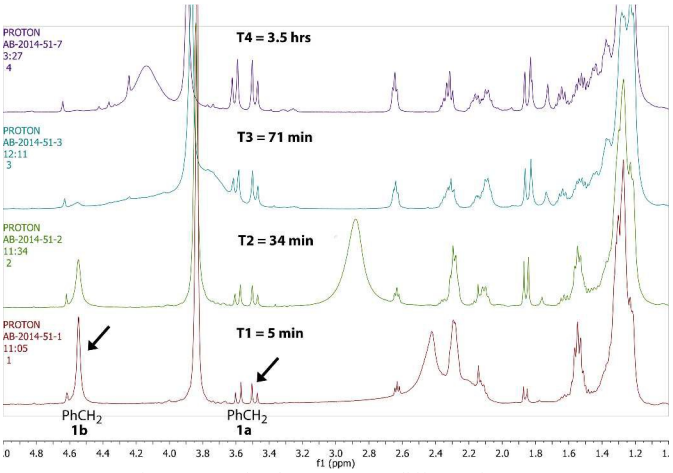


Figure 1. Reaction progression by NMR at 4 different times.

The diaziridine ring shares a particular set of properties. It is a hydrazine and aminal at the same time. Moreover, due to ring strain and lone-pair repulsion; both *N* atoms are configurationally stable.[15] We clearly observe this particular phenomenon in the diaziridination of cyclohexanone. The respective diaziridine is only chiral at the *N* atoms and its benzylic protons in the ^{1}H-NMR were shown to be diastereotopic (Supporting Information). Thus, all the diaziridines obtained as single isomers were obtained as a single diastereomers. We then turned our attention to further understanding the mechanism for this reaction. Although it has been postulated that this reaction undergoes imine formation followed by diaziridination, we sought to determine if the diaziridination step was concerted or stepwise.[16] Thus, we designed an experiment to follow the reaction completion at low temperature by NMR (**Figure 1**).[17] This experiment shows that imine **1b** benzylic protons form immediately upon mixing the aldehyde with the amine (singlet at 4.55 ppm, reaction time = 5 min, red spectrum), with trace amounts of diaziridine **1a** diastereotopic benzylic protons (doublet of doublets at 3.55 ppm). As the reaction moves forward (spectrum in green, blue and purple), the ratio of these benzylic protons shifts to the complete disappearance of imine **1b** benzylic protons after 3.5 h. The new resonance corresponds to the benzylic protons in the diaziridine ring in a *trans* stereochemical relationship to the alkyl chain from the aldehyde substrate.[18] Throughout the duration of this experiment, we did not observe the formation of non-chiral intermediates. These results indicate that the diastereoselective step may be a concerted step; however, a pathway going through a highly organized ionic transition state towards the formation of the diaziridine product is also viable given the experimental results.

Conclusions

We have created a proficient and general method for the synthesis of substituted diaziridines. This reaction constructs three stereocenters in one step from achiral substrates. Furthermore, this method efficiently provides the desired heterocycle for a wide variety of aromatic and aliphatic aldehydes, ketones and amines. We will continue to focus on further understanding the reaction pathway leading to these diaziridines. Moreover, the substituted diaziridines made through these efforts will be assayed as potential cytochrome P450 2B6 inhibitors to gain insight into the pharmacological profile of this scaffold.

Acknowledgements

The Donors of the American Chemical Society Petroleum Research Fund financially supported these research efforts. We are also thankful to Mr Steven M. Ruggiero for his participation.

Notes and references

§ Department of Chemistry and Biochemistry, Rowan University, 201 Mullica Hill Rd, Glassboro, New Jersey, USA. E-mail: **mouraletts@rowan.edu**

Electronic Supplementary Information (ESI) available: [Experimental protocols and spectroscopic data for each diaziridine are provided]. See DOI: 10.1039/c000000x/

1 *Asymmetric Synthesis of Nitrogen Heterocycles,* Ed. J. Royer, Wiley-VCH: Wienheim, 2009.
2 *The Chemistry of Heterocycles;* Ed. Eicher, T.; Hauptmann, S. Wiley-VCH: 2005.
3 For reviews, see: (a) H. Chuang-Yang and A. G. Doyle, *Chem. Rev.* 2014, ***114***, 8153. (b) R. A. Moss, *Acc. Chem. Res.* 2006, ***39***, 267. (c) Y. Zhu, R. C. Cornwall, H. Du, B. Zhao and Y. Shi, *Acc. Chem. Res.* 2014, ***47***, 3665. (d) Liu, Ed. *Chemistry of Diazirines*, Ed. M. T. H. Liu, CRC Press: Boca Raton, FL, 1987.
4 H. Ishihara, K. Hori, H. Sugihara, Y. N. Ito and T. Katsuki, *Helv. Chim. Acta,* 2002, ***85***, 4272.
5 Y. Schneider, J. Prevost, M. Gobin and C. Y. Legault, *Org. Lett.* 2014, ***16***, 596.
6 (a) H. Du, B. Zhao and Y. Shi, *J. Am. Chem. Soc.* 2007, ***129***, 762. (b) B. Zhao, H. Du and Y. Shi, *J. Am. Chem. Soc.* 2008, ***130***, 7220.
7 (a) D. A. Capretto, C. Brouwer, C. B. Poor and C. Hue, *Org. Lett.* 2011, ***13***, 5842. (b) A. V. Shevtsov, V. V. Kuznetsov, A. A. Kislukhin, V. Y. Petukhova, Y. A. Strelenko and N. N. Makhova, *J. Heterocycl. Chem.*, 2006, ***43***, 881. (c) H. Du, B. Zhao and Y. Shi, *J. Am. Chem. Soc.*, 2007, ***129***, 762. (d) B. Zhao, H. Du, S. Cui and Y. Shi, *J. Am. Chem. Soc.,* 2010, ***132***, 3523. (e) B. Zhao, X. Peng, S. Cui and Y. Shi. *J. Am. Chem. Soc.,* 2010, ***132***, 11009.
8 (a) Y. Kobayashi, C. Sridar, U. M. Kent, S. G. Puppali, J. M. Rimoldi, H. Zhang, L. Waskell and P. F. Hollenberg, *Drug Met. And Dispos.,* 2006, ***34***, 2102. (b) C. Sridar, Y. Kobayashi, H. Brevig, U.

M. Kent, S. G. Puppali, J. M. Rimoldi and P. F. Hollenberg, *Drug Met. And Dispos.,* 2006, ***34***, 1849.

9 (a) E. Schmitz, *Angew. Chem.*, 1959, ***71***, 127. (b) H. J. Abendroth and G. Henrich, *Angew. Chem.*, 1959, ***71***, 283. (c) R. S. Paulsen, *Belg. Pat.,* 1959, ***58***, 8352.

10 (a) L. Carroccia, S. Fioravanti, L. Pellacani, C. Sadun and P. A. Tardella, *Tetrahedron,* 2011, ***67***, 5375. (b) N. N. Makhova, V. Y. Petukhova and V. V. Kuznetsov, *ARKIVOC*, 2008, 128.

11 L. Lykke, K. S. Halskov, B. D. Carlsen, V. X. Chen and K. A. Jorgensen, *J. Am. Chem. Soc.* 2013, ***135***, 4692. Other methods using chiral imines: (a) S. Fioravanti, L. Olivieri, L. Pellacani and P. A. Tardella, *Tetrahedron Lett.*, 1998, ***39***, 6391. (b) L. Carrocia, M. Delfini, S. Fioravanti, L. Pellacani and F. Sciubba, *J. Org. Chem.* 2012, ***77***, 2069.

12 M. B. Mohamed and J. Parrick, *Org. Prep. Proc. Int.,* 1981, ***13***, 371.

13 The relative stereochemistry between each chiral *N* was assigned to be *trans* based on lone-pair repulsion. The relative stereochemistry between the substituents in position 1 and 3 should favour the trans isomer by up to 8 kcal/mol (see reference 11). The relative stereochemistry was confirmed by NOESY experiments. O. Trapp, V. Schurig and R. G. Kostyanovsky, *Chem. Eur. J.,* 2004, ***10***, 951.

14 The following aromatic ketones failed to provide the corresponding diaziridines (acetophenone, 4'-methoxyacetophenone and α-tetralone).

15 (a) W. B. Jennings, D. R. Boyd, In *Cyclic Organonitrogen Stereodynamics*; J. B. Lambert, Y. Takeuchi, Eds, VCH: New York, 1992, Chapter 5. (b) R. G. Kostyanovsky, G. V. Shustov and V. V. Starovoitov, *Mendeleev Comm.,* 1998, ***8***, 113. (c) O. Trapp, L. Sahraoui, W. Hofstadt and W. Konen, *Chirality*, 2010, ***22***, 284.

16 It has been previously proposed that diaziridination of the respective imine involves an ionic pathway: Initial nucleophilic addition followed by ring closure (reference 11a). However, no direct evidence disproving a concerted pathway (addition of HOSA across imine bond) has been reported.

17 Diaziridination in NMR tube was ran with $CDCl_3$ at 0.1 M concentration between benzylamine (3 equiv.) and hydrocinnamaldehyde (1 equiv.).

18 K. Zawatzky, M. Kamuf and O. Trapp, *Chirality*, 2015, ***27***, 156.