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Solid-Phase Synthesis of Polysubstituted Piperidines by Imino-Diels–Alder Cycloaddition of 2-Amino-1,3-butadienes with Solid-Supported Imines

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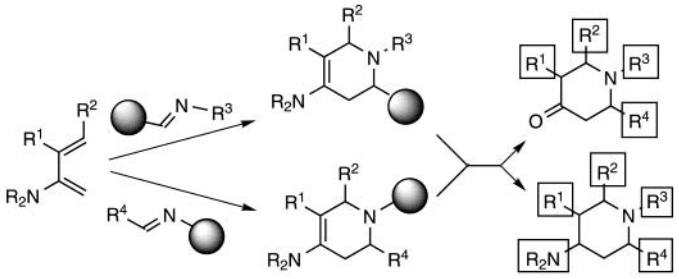
ABSTRACT



The solid-phase imino-Diels–Alder reaction of 2-amino-1,3-butadienes with solid-supported imines is described. The reaction furnishes 4-piperidones and 4-aminopiperidines with high diastereoselectivity and with very good yields and purity after the release from the solid support. The possibility of introducing variations in both cycloaddition partners gives rise to substituted piperidines with up to five elements of diversity.

Combinatorial chemistry has emerged as a powerful tool for drug discovery.[1] Solid-phase organic synthesis originally developed in peptide chemistry is now widely accepted as the major methodology because it offers the opportunity for rapidly synthesizing large numbers of druglike molecules without tedious and time-consuming purification steps. Therefore, the development of new strategies for carbon−carbon bond formation reactions on solid support has become urgent.[2]

Among the most important carbon−carbon bond forming reactions available, the Diels−Alder reaction, 75 years after its discovery, continues to be one of the most suitable processes for constructing six-membered ring systems.[3] Moreover, cycloaddition reactions may offer wide scope in the generation of molecular diversity through the variation of the structure of both reactants, diene and dienophile. Despite this potential, not many examples of the application of the Diels−Alder reaction in solid phase have been reported in the literature when compared with the synthetic versatility of this reaction in solution.[4,5] In fact, very little effort has been dedicated to the generation of diversity by variation of

(1) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477−517 and references therein.

(2) For recent reviews, see: (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (b) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202.

(3) For some recent excellent reviews on the Diels−Alder reaction, see: (a) Corey E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667. (b) Nicolau, K. C.; Snyder, S. A.; Montagnon, T.; Vassiligiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(4) For a review about Diels−Alder reactions on solid-phase: Yli-Kauhaluoma, J. *Tetrahedron* **2001**, *57*, 7053−7071.

(5) For examples of inverse electron demand [4 + 2] heterocycloadditions, see: (a) Tietze, L. F.; Hippe, T.; Steinmetz, A. *Synlett* **1996**, 1043−1044. (b) Leconte, S.; Durjadin, G.; Brown, E. *Eur. J. Org. Chem.* **2000**, 639−643. (c) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3417−3421.

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the structure of the diene, since most of the work of solid-phase Diels−Alder chemistry has been generally restricted to silyloxydienes, mainly to Danishefsky's diene.[6,7]

Our group has been working for many years in the synthesis, reactivity, and synthetic applications of 2-amino-1,3-butadienes.[8] We have shown that these dienes possess important features in the Diels−Alder reaction: their high reactivity permits mild conditions, and a high degree of regio-, diastereo-, and enantioselectivity can be achieved. Moreover, when compared with the notorious Danishefsky's diene, they can provide a wider range of different substituents that conduct to highly functionalized products. We have recently reported enantioselective convergent approaches to unnatural amino acids and natural alkaloid scaffolds starting from [4 + 2] cycloadditions with 2-amino-1,3-butadienes.[9] Polymer-bound 2-amino-1,3-butadienes have been previously employed in solid-phase synthesis;[10] however, to the best of our knowledge, the reactions of aminodienes with solid-supported dienophiles remain unstudied.

On the basis of our previous experience in solution phase we decided to explore the applicability of these systems in the Diels−Alder reaction with solid-supported dienophiles. A very attractive reaction of 2-amino-1,3-butadienes is the imino-Diels−Alder cycloaddition, which gives rise to functionalized piperidines with very high diastereoselectivity.[9] Moreover, this reaction offers the opportunity to introduce diversity elements in both cycloaddition counterparts, the solid-supported imine and the diene.[11] Substituted piperidines are present in a very large number of natural products and pharmaceuticals, and therefore the development of solid-phase methods that may allow the easy synthesis of libraries is of great interest.

In this communication, we report our findings toward the development of a general method for the solid-phase synthesis of highly substituted piperidines, formed by imino-Diels−Alder reaction between resin-bound imines and 2-amino-1,3-butadienes (Figure 1).[12]

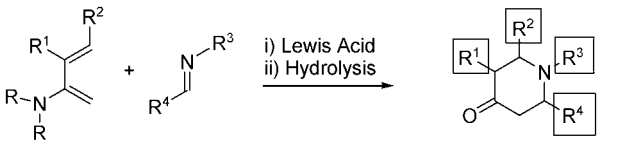


Figure 1. Imino-Diels−Alder reaction of 2-amino-1,3-butadienes. Potential diversity points are highlighted.

The polymer-bound imines were prepared using already described protocols, following two different approaches. Nitrogen-bound imines **2** were synthesized by condensation of Kobayashi's BOBA (*p*-benzyloxybenzylamine) resin[13] with different aromatic aldehydes employing trimethyl orthoformate as desiccant.[14] In this manner, imines from aromatic aldehydes with electron-donating as well as electron-withdrawing groups and heteroaromatic aldehydes were furnished. Carbon-bound imines **2′** were prepared as reported in the literature from a *p*-hydroxybenzaldehyde-modified Wang resin (Figure 2).[6b]

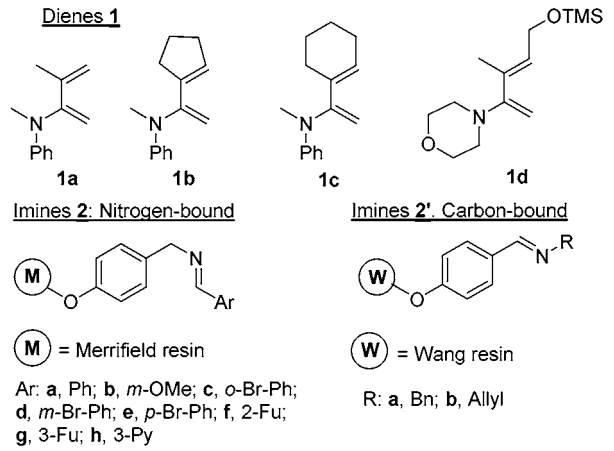


Figure 2. 2-Amino-1,3-butadienes **1** and imines **2** and **2′** used.

The 2-amino-1,3-butadienes **1** employed were readily prepared using the mercury-assisted hydroamination of enynes.[15] Both *N*-methylaniline and morpholine-substituted 2-aminodienes were used (Figure 2).

The initial studies were carried out under reaction conditions that had been previously developed for the solution-phase cycloaddition of diene **1d** with aldimines.[9e] To avoid the possible formation of diastereoisomers coming from the cycloaddition, we started our study with the less substituted aminodiene **1a**. Thus, diene **1a** was added to the preswelled resin **2a** (Ar = Ph) in THF in the presence of a catalytic amount of $Yb(OTf)_3$ under an inert atmosphere. After 12 h at room temperature, we observed variation in the IR spectra

(6) For some examples of reactions of silyloxy dienes with solid-supported dienophiles, see: (a) Creighton, C. J.; Zapf, C. W.; Bu, J. H.; Goodman, M. *Org. Lett.* **1999**, *1*, 1407−1409. (b) Wang, Y.; Wilson, S. R. *Tetrahedron Lett.* **1997**, *38*, 4021−4024.

(7) For solid-supported silyloxydienes and their use in Diels−Alder cycloadditions, see: Smith, E. M. *Tetrahedron Lett.* **1999**, *40*, 3285−3288.

(8) For reviews on the Diels−Alder reaction of amino-substituted dienes, see: (a) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023−1035. (b) Barluenga, J.; Suarez-Sobrino, A.; Lopez, L. A. *Aldrichimica Acta* **1997**, *32*, 4−15.

(9) (a) Barluenga, J.; Aznar F.; Valdés, C.; Cabal M. P. *J. Org. Chem.* **1993**, *58*, 3391−3396. (b) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403−4404. (c) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M. P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805−811. (d) Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. *J. Org. Chem.* **1998**, *63*, 3918−3924. (e) Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Org. Lett.* **2002**, *4*, 1971−1974.

(10) Crawshaw, M.; Hird, N. W.; Irie, K.; Nagai, K. *Tetrahedron Lett.* **1997**, *38*, 7115−7118.

(11) Very recently we have shown that 2-aminodienes with different types of substituents in the diene skeleton can participate in the imino-Diels−Alder cycloaddition in solution phase: Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. Submitted for publication.

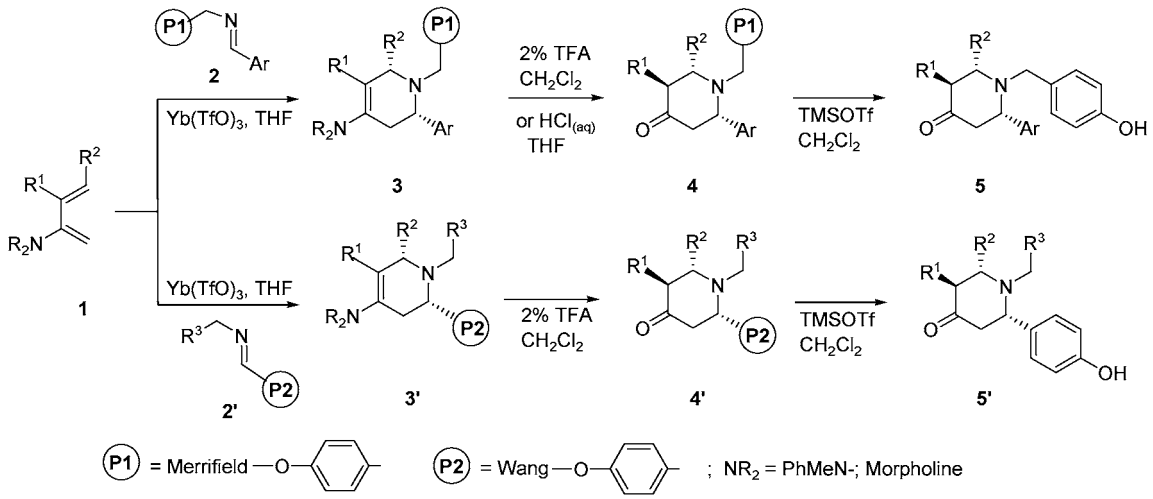
(12) For previous examples of solid-phase imino-Diels−Alder reactions, see: (a) Reference 6b. (b) Zang, W.; Wenhua, X.; Fang, J.; Wang, P. G. *Tetrahedron Lett.* **1999**, *40*, 7929−7933.

(13) Kobayashi, S.; Auki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345−7348.

(14) Look, G. C.; Murphy M. M.; Campbell. D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937−2940.

(15) Barluenga, J.; Aznar, F.; Valdés, C.; Cabal, M. P. *J. Org. Chem.* **1991**, *56*, 6166−6171.

Scheme 1. Solid-Phase Synthesis of 4-Piperidones **5** and **5′**



of the resin before and after the cycloaddition, which indicated that a reaction may have occurred on the polymer. The cleavage of the cycloadduct from the resin was attempted by treatment with different mixtures of TFA/CH_2Cl_2, but no cycloaddition product was detected after the cleavage, probably as a result of decomposition of the adduct under the strong acidic conditions.[16] Then, we moved to the published cleavage method for BOBA resin, which consisted in the utilization of TMSOTf,[13] a less acidic Lewis acid. This time, we obtained a reaction mixture from which the expected 4-piperidone could be detected, although with low purity and yield, together with some silylated species. To avoid the presence of these undesired products, we decided to carry out the hydrolysis of the enamine **3**, which would furnish solid-supported 4-piperidone **4**, before the release of the cycloadduct from the resin. Therefore, resin **3aa** was treated with a 2% TFA solution in CH_2Cl_2, to afford solid-supported piperidone **4aa**,[17] which upon cleavage by treatment with TMSOTf followed by an aqueous $NaHCO_3/CH_2Cl_2$ extraction of the filtrate afforded piperidone **5aa** with good yield and purity as a single diastereoisomer (Scheme 1).

The reaction was then extended to solid-supported imines **2** and **2′** and aminodienes **1**, affording in most of the examples the desired 4-piperidones **5** and **5′** with good yields and purities (Scheme 1, Table 1). It should be pointed out that in the course of the reaction sequence up to three stereogenic centers can be created, therefore, the stereoselectivity of the process is an additional issue that must be taken into account.

For instance, the temperature must be lowered to −60 °C to achieve total diastereoselectivity in the cycloaddition step when the six-membered ring diene **1c** was employed (a 1:1 mixture of diastereoisomers was obtained when the reaction was conducted at room temperature). However, −90 °C was not sufficient to avoid the formation of two diastereoisomers (4:1) in the case of diene **1b** (1:1 mixture at room temperature).[18] On the other hand, for those adducts coming from imines **2f** and **2g**, derived from 2-furaldehyde and 3-furaldehyde, respectively, hydrolysis of the enaminic adducts employing the standard 2% TFA/CH_2Cl_2 solution furnished a mixture of epimers of C3. Nevertheless, after intense experimentation, it was found that treatment of resin **3** with an extremely diluted hydrochloric acid solution in THF (0.1 mL of aqueous 0.01 N HCl in 3.5 mL of THF), followed by the standard cleavage protocol described above, allows for the isolation of a single diastereoisomer of the furyl-substituted 4-piperidones **5af** and **5ag**.

The scope of the cycloaddition reaction described above is summarized in Table 1. Dienes with different substituents and functionalization can be employed. The structure of the imines can also be very diverse. In this account we have studied the reaction with imines derived from electron-rich, bromosubstituted[19] aromatic and also heteroaromatic aldehydes. Moreover, the reaction is compatible with the attachment of the imine to the solid support at both the N- or C-terminus, increasing the number of points of diversity.

So far, we have described the synthesis of 4-piperidones **5** and **5′** by release of the cycloadduct from the solid support. However, it is worth noting that 4-aminotetrahydropiridines **3** and **3′** and 4-piperidones **4** and **4′** are substrates that could

(16) We knew from our previous work (ref 9b,c) in solution-phase imino-Diels−Alder reactions of 2-amino-1,3-butadienes that 4-aminotetrahydropiridines may undergo decomposition upon treatment with aqueous acidic solutions, and therefore hydrolysis of the enamine functionality to yield 4-piperidones must be carried out under very mild acidic conditions, usually by filtration through SiO_2 short columns (a methodology that is obviously not possible in solid phase).

(17) Careful removal of the solvent of the filtrate of the hydrolytic step gave rise to a residue that consisted of *N*-methylaniline as the unique organic compound, which indicated that, in fact, hydrolysis of the enamine had been achieved.

(18) Lower yields and no stereoselectivity improvement were obtained when different Lewis acids [$Cu(OTf)_2$, $CuClO_4$, $Sc(OTf)_3$, $ZnCl_2$] were used in the cycloaddition.

(19) Bromosubstituted aromatic rings are particularly attractive in diversity-oriented synthesis because they can be easily transformed into differently substituted aromatics by cross-coupling reactions that have been well-established in solid phase. See, for instance: (a) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993−6996. (b) Chamoin, S.; Houldsworth, S.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4175−4178.

Table 1. 4-Piperidones **5** and **5′** Synthesized in Solid Phase

	R^1	R^2	R^3	Ar	yield %[b]	purity%[c]
5aa	CH_3	H	*p*-HO-Ph	Ph	93	89
5ab	CH_3	H	*p*-HO-Ph	*m*-MeO-Ph	80	80
5ac	CH_3	H	*p*-HO-Ph	*o*-Br-Ph	83	99
5ad	CH_3	H	*p*-HO-Ph	*m*-Br-Ph	91	92
5ae	CH_3	H	*p*-HO-Ph	*p*-Br-Ph	67	89
5af	CH_3	H	*p*-HO-Ph	2-furyl	71	87
5ag	CH_3	H	*p*-HO-Ph	3-furyl	76	90
5ah	CH_3	H	*p*-HO-Ph	3-Py	71	83
5ba	-$(CH_2)_3$-		*p*-HO-Ph	Ph	78[d]	
5ca	-$(CH_2)_4$-		*p*-HO-Ph	Ph	90[f]	92
5da	CH_3	CH_2OH	*p*-HO-Ph	Ph	82[g]	85
5′aa	CH_3	H	Bn	*p*-HO-Ph	54	88
5′ab	CH_3	H	allyl	*p*-HO-Ph	66	94
5′ba	-$(CH_2)_3$-		Bn	*p*-HO-Ph	42[e,d]	
5′ca	-$(CH_2)_4$-		Bn	*p*-HO-Ph	59	88

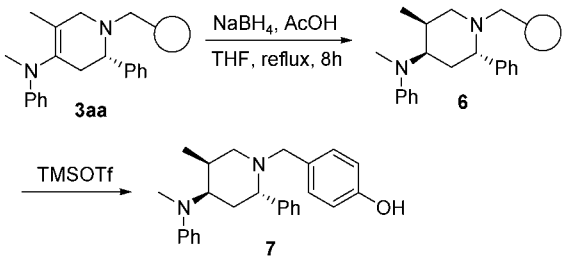
[a] All compounds gave satisfactory ^{1}H and ^{13}C NMR and HRMS data. The stereochemical arrangement of the substituents was determined by bidimensional NMR studies. [b] Based on loading of BOBA resin as judged by Fmoc reading for nitrogen-bound imines and based on initial Wang resin loading for carbon-bound imines. [c] Calculated from integrated peak areas recorded by the HPLC analysis (220 nm) of the crude products. [d] Obtained as a mixture of diastereoisomers. [e] Reaction carried out at −90 °C. [f] Reaction carried out at −60 °C. [g] Reaction carried out with 2-morpholino-1,3-butadiene **1d**.

be chemically modified prior to their release from the resin to increase the molecular diversity.

As an example of this additional possibility, the reduction of the enaminic adducts **3**, which would furnish 4-aminopiperidines, was examined. Different protocols using various reducing agents were tried with a model enamine in solution, and the best results were obtained with a solution of $NaBH_4$ and AcOH in THF. The same reaction conditions were applied to solid-supported 4-aminotetrahydropiridine **3aa** to obtain, after release from the resin, the 4-aminopiperidine **7** with total diastereoselectivity and moderate yield (46% after purification by chromatography) and purity (Scheme 2).[20]

(20) The stereochemical arrangement of the stereogenic centers of **7** was deduced by ^{1}H and ^{13}C NMR bidimensional studies.

Scheme 2. Solid-Phase Reduction of Enamine **3aa**. Synthesis of 4-Aminopiperidine **7**



Including this feature, the number of elements of diversity could be enhanced by using different amines in the diene synthesis.

In conclusion, we have developed a model protocol for the solid-phase parallel synthesis of polysubstituted piperidines from readily accessible starting materials with a high degree of diversity. This methodology has proven in general to be a valuable strategy because it permits facile variation of substituents in the core ring. The overall yields and purities suggest that the method is sufficiently general to accommodate a wider variety of substituents and the simplicity of the operations would lead to easy automation. Moreover, the possibility of carrying out chemical transformations on the cycloadducts before the release from the polymer allows for the introduction of additional diversity in the piperidine scaffold.

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Supporting Information Available: Experimental procedures and full characterization data of piperidones **5** and **5′** and 4-aminopiperidine **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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