Intermolecular Polar [4π⁺ + 2π] Cycloadditions of Cationic 2-Azabutadienes from Thiomethylamines: A New and Efficient Method for the Regio- and Diastereo-selective Synthesis of 1,2,3,4-Tetrahydroquinolines

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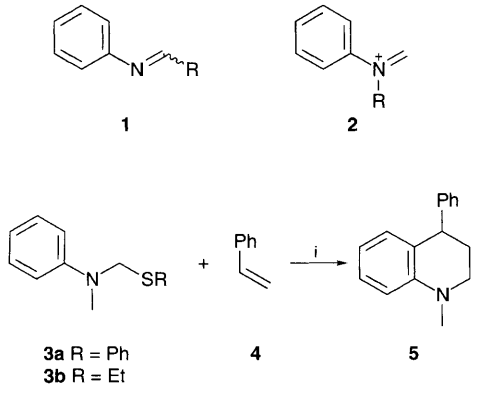
Substituted 1,2,3,4-tetrahydroquinolines and related condensed nitrogen-heterocycles are formed highly regio- and diastereo-selectively with yields ranging from 57 to 100% by intermolecular polar [4π⁺ + 2π] cycloadditions of cationic 2-azabutadienes from thiomethylamines and various dienophiles.

Substituted 1,2,3,4-tetrahydroquinolines, which play an important role in the preparation of natural products and medically interesting compounds,[1] can be synthesized by intermolecular cycloadditions of neutral or cationic 2-azabutadienes with electron-rich alkenes.[2] In most cases *N*-arylimines **1** have been employed as preformed neutral 2-azabutadienes.[3] But, from semiempirical calculations of their LUMO energies and their p-atomic orbital coefficients† it becomes clear that positively charged 2-azabutadienes **2** are considerably more reactive and selective than their neutral counterparts **1**, which usually need to be activated by Lewis acids and/or electron-withdrawing groups (EWG) (**1**, R = EWG).[2,3]

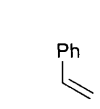
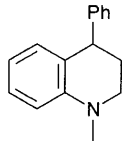
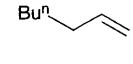
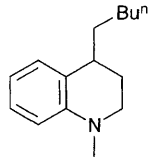
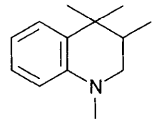
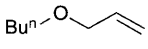
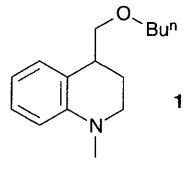
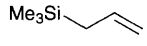
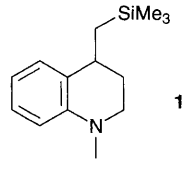
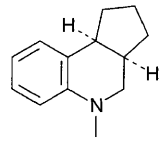
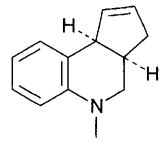
Cationic 2-azabutadienes **2** are generated *in situ* by condensation of anilines with carbonyl compounds under acidic conditions[4] or by heterolytic cleavage of α-heterosubstituted anilines.[5] So far, mainly oxymethylamines have been used as precursors, but they can be synthesized efficiently only by anodic oxidation.[5a,b] The reactions of cationic 2-azabutadienes **2** with alkenes may either proceed as one-step concerted polar [4π⁺ + 2π] cycloadditions[2,6] or as two-step intermolecular 1,2-C=N⁺ addition[7]–intramolecular cationic cyclization[8] sequences. Little is known about the mechanism and stereoselectivity of the process in question and the few results available point to a two-step mechanism involving cationic intermediates.[4b,c,5b]

Here, we report on a new and efficient method for the highly regio- and diastereo-selective preparation of 3,4-disubstituted 1,2,3,4-tetrahydroquinolines that rests on the unprecedented *in situ* generation of cationic 2-azabutadienes from thiomethylamines easily available by reactions of anilines with formaldehyde and thiols.[9] Hence the stable **3a**‡ was prepared with 84% yield.[10] We found that the cleavage of **3a** to generate the charged 2-azabutadiene **2** (R = Me) and its subsequent reaction with alkenes can be effected by a number of Lewis acids including $BF_3{\cdot}Et_2O$, $TiCl_4$ and $SnCl_4$. For example, treatment of **3a** and styrene **4** (1.5 equiv.) with $SnCl_4$ (1.0 equiv.) at −78 °C gave 61% of **5**. The yield of **5** was improved to 81% by simply raising the reaction temperature to 25 °C. Finally, a 100% yield of **5** was obtained when a 2:1 mixture of $TiCl_4$ and triphenylphosphane in CH_2Cl_2 was used as Lewis acid (Scheme 1). It is remarkable that a 1:1 mixture of the reagents§ gives no product at all. Use of the ethylthio derivative **3b** as substrate led to **5** in 80% yield (Scheme 1).

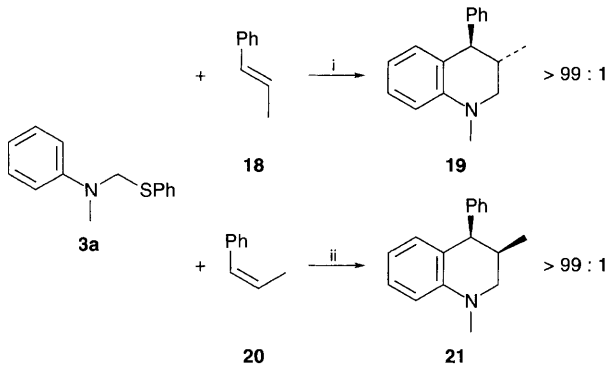


Scheme 1 *Reagents and conditions*: i, $TiCl_4:PPh_3$ = 2:1 (2.0 equiv.), **4** (1.5 equiv.), CH_2Cl_2, 0 °C, 10 min, then room temp., 72 h, 100% (with **3a**), 80% (with **3b**)

Table 1 Reactions of the thiomethylamine **3a** with dienophiles using a 2:1 mixture of $TiCl_4$ and PPh_3 as Lewis acid[a]

Entry	Dienophile		*t*/h	Product		Yield (%)[b]
1		**4**	72		**5**	100
2		**6**	72		**7**	57
3		**8**	120		**9**	74
4		**10**	72		**11**	72
5		**12**	72		**13**	67
6		**14**	120		**15**[c]	87
7		**16**	48		**17**[c]	79

[a] Dienophile (1.5 equiv.), $TiCl_4:PPh_3$ = 2:1 (2.0 equiv.), room temp. [b] After column chromatography. [c] The diastereoisomeric purity was determined by ^1H NMR.



Scheme 2 *Reagents and conditions*: i, $TiCl_4$: PPh_3 = 2 : 1 (2.0 equiv.), **18** (1.5 equiv.), CH_2Cl_2, 0 °C, 10 min, then room temp., 72 h, 75%; ii, $TiCl_4$: PPh_3 = 2 : 1 (2.0 equiv.), **20** (1.5 equiv.), CH_2Cl_2, 0 °C, 10 min, then room temp., 72 h, 67%. The diastereoisomeric purity of **18** and **20** was determined by GC and GC-MS, and that of **19** and **21** was determined by ^1H NMR, HPLC, and GC-MS

Various alkenes were treated with **3a** using a 2 : 1 mixture of $TiCl_4$ and triphenylphosphane as Lewis acid to yield the corresponding tetrahydroquinolines. These were obtained regiospecifically and diastereoisomerically pure with yields ranging from 57 to 100% (Table 1). In particular, it was shown that acyclic alkenes **6** and **8** (Table 1, entries 2, 3) as well as functionalized alkenes like the allyl ether **10** and the allylsilane **12** (Table 1, entries 4, 5) could be used as dienophiles. With cyclic alkenes like cyclopentene **14** and cyclopentadiene **16** the cyclopenta[*c*]quinolines **15** and **17** were obtained (Table 1, entries 6, 7).

From a synthetic as well as mechanistic point of view the transformations of **3a** with (*E*)- and (*Z*)-methylstyrene **18** and **20** are particularly interesting. The reaction of (*E*)-methylstyrene **18** exclusively gave the *trans*-product **19**¶ while the reaction of (*Z*)-methylstyrene **20** yielded the diastereoisomerically pure *cis*-product **21**** indicating that the stereochemistry of the olefinic dienophiles **18** and **20** is completely retained during the reactions (Scheme 2). From AM1 and PM3 calculations† it follows that the *trans*-tetrahydroquinoline **19** is more stable than the *cis*-compound **21**, irrespective of the pseudoequatorial and pseudoaxial position of the 4-phenyl and the 3-methyl group. These results can best be rationalized in terms of a one-step concerted [$4\pi^+ + 2\pi$] cycloaddition,[2,6] a view that is further supported by the fact that no side products could be isolated in any of the reactions that might have originated from possible cationic intermediates. Regardless of the mechanism operative a new and efficient method for the preparation of regiospecifically and diastereoisomerically pure 3,4-disubstituted 1,2,3,4-tetrahydroquinolines and cyclopenta[*c*]quinolines has been developed.

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Footnotes

† Calculations were performed using the VAMP and MOPAC 6.0 packages. VAMP (T. Clark, Universität Erlangen-Nürnberg) is a vectorized version of AMPAC and MOPAC. The keyword PRECISE was used throughout.

‡ Satisfactory analytical (combustion and/or high-resolution mass) and spectral (UV, IR, ^1H NMR, ^{13}C NMR, and MS) data were obtained for all compounds.

§ A 1 : 1 mixture of $TiCl_4$ and triphenylphosphane has been used as the Lewis acid to promote aldol reactions[11a] and the addition of allylic nucleophiles to acetals.[11b]

¶ *Selected data for* **19**: δ_H (300 MHz; CD_3SOCD_3; Me_4Si; *J* in Hz) 0.83 (3 H, d, 3-Me_{eq}), 2.13 (1 H, m, 3-H_{ax}), 2.86 (3 H, s, NMe), 2.94 (1 H, dd, *J* 8.5 and 11, 2-H_{ax}), 3.18 (1 H, dd, *J* 4 and 11, 2-H_{eq}), 3.64 (1 H, d, *J* 8.5, 4-H_{ax}), 6.40–6.46 (2 H, m, 6-H, 7-H), 6.64 (1 H, d, *J* 8, 8-H), 6.94–7.32 (6 H, m, 5-H, and 5 × phenyl H).

** *Selected data for* **21**: δ_H (200 MHz; CD_3SOCD_3; Me_4Si; *J* in Hz) 0.70 (3 H, d, *J* 7, 3-Me_{ax}), 2.26 (1 H, m, 3-H_{eq}), 2.92 (1 H, d, *J* 11, 2-H_{ax}), 2.93 (3 H, s, NMe), 3.03 (1 H, ddd, *J* 1.5, 4.5 and 11, 2-H_{eq}), 3.98 (1 H, d, *J* 5, 4-H_{ax}), 6.47 (1 H, dt, *J* 1 and 7.5, 6-H), 6.67 (1 H, dd, *J* 1 and 8, 8-H), 6.74 (1 H, dd, *J* 2 and 7.5, 5-H), 6.95–7.29 (6 H, m, 7-H, and 5 × phenyl H).

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