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Acid-catalyzed cyclization of acyliminium ions derived from allenamides. A new entry to protoberberines

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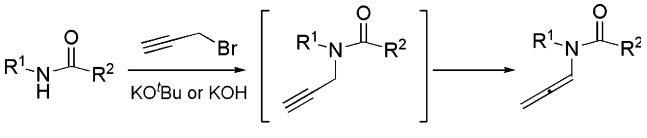
Abstract—Under mild acidic conditions, *N*-(ω-phenylalkyl)allenamides can yield stabilized acyliminium ions which through intramolecular aromatic electrophilic substitution furnish 1-vinylisoindolines and isoquinolines. Stereoelectronic and entropic effects in these cyclizations have been evaluated by DFT computations. The 1-vinylisoquinolines obtained have been employed as key intermediates in the synthesis of the protoberberine skeleton.

Allenamide chemistry[1] has received considerable attention in recent years,[2] with exploration of the reactivity of allenamides in transition-metal catalyzed cyclization,[3] [2+2] and inverse demand [4+2] cycloadditions,[4] and other cyclization reactions.[5] Allenamides (**3**) are commonly prepared by a tandem reaction in which condensation of propargyl bromide with a secondary amide (**1**) is followed by base-catalyzed isomerization of the resulting propargylamide (**2**) (Scheme 1), although under these conditions the resulting allenamides sometimes evolve further to ynamides.[2a] Due to allylic stabilization of the intermediates, these electron-deficient allenamines are highly susceptible to nucleophilic, electrophilic, and even radical addition[6] at the central sp carbon atom.

In this Letter we describe a new cyclization reaction based on the formation of an acyliminium ion[7] by treatment of an appropriate allenamide with trifluoroacetic acid. The reaction was developed and investigated using allenamides **3a–e** (Table 1), which were prepared in 50–90% overall yield by reaction of the corresponding amines with an acylating agent followed by treatment with propargyl bromide in the presence of a base.[8]



1 **2** **3**

Scheme 1.

Treatment of allenamides **3** with a catalytic amount of TFA in dichloromethane at room temperature afforded the vinyl-substituted heterocyclic compounds **5** in moderate to good yields,[9] presumably through protonation of the allenamide followed by intramolecular electrophilic aromatic substitution on the electron-rich arene of the resulting acyliminium ion (**4**) (Scheme 2). That these reactions take place under such mild conditions can undoubtedly be attributed to the allylic nature of the intermediate cations **4**.

In the first of these cyclizations, treatment of benzylallenamide **3a** with a catalytic amount of TFA afforded the

Table 1. Yields in the preparation and acid-catalyzed cyclization of allenamides **3a–e**

Compound	*n*	R^1	R^2	% Yield of **3**	% Yield of **5**
a	0	MeO	H	50	22
b	1	MeO	H	85	67
c	1	H	H	63	—
d	1	MeO	2-I-Phenyl	74	78
e	2	MeO	H	81	—

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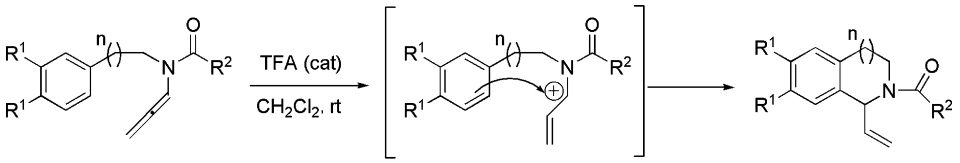
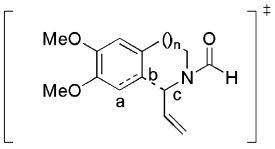


3 4 5

Scheme 2.

Table 2. Activation barrriers (kcal/mol) and relevant geometric parameters for the cyclization of allenamides **3a**, **3b** and **3e**

Structure	$\Delta H_0^{\dagger}$	$\Delta G_{298.15}^{\dagger}$ (Gas-phase)	$\Delta G_{298.15}^{\dagger}$ (CH_2Cl_2)
TS-**4a**	15.8	17.4	17.3
TS-**4b**	0.9	4.4	9.0
TS-**4e**	7.5	12.0	18.8

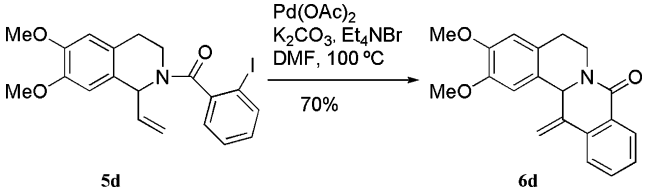


TS-**4a**	R_{bc} = 2.068 Å	Θ_{abc}=122.1°
TS-**4b**	R_{bc} = 2.034 Å	Θ_{abc}=109.4°
TS-**4e**	R_{bc} = 2.007Å	Θ_{abc}=109.5°

desired vinyl isoindoline **5a**, but only in low yield (22%). Much better yield was achieved with the phenethyl compounds **3b** and **3d**, which afforded vinyl isoquinolines **5b** and **5d** in 67% and 78% yield, respectively.[10] That the aromatic ring must be electron-rich was shown by the failure of allenamide **3c** to cyclize even under harsher conditions (50% TFA, DMF, 70 °C). The homologous compound **3e** also failed to cyclize under the standard reaction conditions, and raising the temperature to 60 °C resulted in hydrolysis to the secondary amide.

Suspecting that the differences in behaviour among homologues **3a**, **3b** and **3e** might be due to stereoelectronic constraints in the aromatic electrophilic substitution step, we investigated this step by computing geometries and energies for intermediates **4a**,**b**,**e** and transition structures TS-**4a**,**b**,**e** at the B3LYP[11]/6-31+G* level. Given their cationic nature, solvation effects were taken into account by performing B3LYP/6-31+G* CH_2Cl_2 PCM[12] single-point computations on the optimized gas-phase structures (Table 2). All computations were performed using the GAUSSIAN03 package.[13]

The computations clearly show that formation of the six-membered ring of **5b** is specially favoured by its allowing perfect alignment of the reaction centres for tetrahedral attack of the positively charged carbon on the arene ($\Theta = 109.4°$) in a chair-like conformation. Thus the gas-phase activation barrier $\Delta G_{298.15}^{\dagger}$ is only 4.4 kcal/mol in TS-**4b**, as against 17.4 kcal/mol in TS-**4a** with a poor alignment between reaction centres ($\Theta = 122.1°$), and 12.0 kcal/mol in TS-**4e**, in which $\Theta = 109.5°$ but greater crowding is present due to an unfavourable axial disposition of the amide group in the crown-chair transition state (geometries can be examined in Supplementary data). When solvation is taken into account, the barriers in TS-**4b** and TS-**4e** are increased due to **4b** and **4e** being more easily solvated than the transition states, but the barrier in TS-**4a** remains virtually unchanged because solvation of **4a** is also inefficient. Unfavourable entropic effects also increase with the length of the phenylalkyl chain of the acyliminium ions, $\Delta G_{298.15}^{\dagger} - \Delta H_0^{\dagger}$ being 1.6, 3.5 and 4.5 kcal/mol for TS-**4a**, TS-**4b** and TS-**4e**, respectively.[14]



5d 6d

Scheme 3.

Finally we observed that the tetracyclic unit of the protoberberine skeleton[15] ought to be easily constructed by a 6-*exo* Heck reaction of an *ortho*-iodobenzamide such as **5d** (Scheme 3), as indeed proved to be the case. When vinylisoquinoline **5d** was heated at 100 °C in DMF in the presence of catalytic $Pd(OAc)_2$, K_2CO_3 as a base and Et_4NBr as an additive, methylene protoberberine **6d** was obtained in 70% yield.[16,17]

In conclusion, allenamides can be used to prepare 1-vinylisoindolines or isoquinolines via acyliminium ions under very mild conditions. The isoquinolines can serve as intermediates in a new synthesis of functionalized protoberberines.

Acknowledgements

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Supplementary data

Cartesian coordinates and energies for all computed structures. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.056.

References and notes

1. For the first allenamides see: (a) Dickinson, W. B.; Lang, P. C. *Tetrahedron Lett.* **1967**, *8*, 3035; (b) Overmann, L. E.; Marlowe, C. K.; Clizbe, L. A. *Tetrahedron Lett.* **1979**, *20*, 599.
2. For reviews on allenamides see: (a) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773; (b) Saalfrank, R. W.; Lurz, C. J. In *Methoden Der Organischen Chemie (Houben Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1993; pp 3093–3102.
3. Gardiner, M.; Grigg, R.; Sridharan, V.; Vicker, R. *Tetrahedron Lett.* **1998**, *39*, 435, and references cited therein.
4. [2+2]: (a) Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T.; Tamaru, Y. *J. Am. Chem. Soc.* **1997**, *119*, 10869, and references cited therein.; [4+2]: (b) Wei, L.-L.; Xiomg, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903; (c) Kimura, M.; Wakamiya, Y.; Horino, Y.; Tamaru, Y. *Tetrahedron Lett.* **1997**, *38*, 3963.
5. (a) Noguchi, M.; Okada, H.; Wantanabe, M.; Okuda, K.; Nakamura, O. *Tetrahedron* **1996**, *52*, 6581; (b) Kant, J.; Farina, V. *Tetrahedron Lett.* **1992**, *33*, 3559–3563.
6. Shen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775.
7. (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367; For allenamide-derived acyliminium ions see: (b) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Challeppan, R.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038.
8. *Typical procedure for the synthesis of allenamides*: KO^{t}Bu (490 mg, 4.01 mmol) and propargyl bromide (330 μL, 4.38 mmol) were added to a solution of *N*-(3,4-dimethoxyphenethyl)-2-iodo benzamide (1.5 g, 3.67 mmol) in 6 mL of dry DMSO and the resulting black solution was stirred at room temperature. Since after 1 h TLC still showed two spots, a further 90 mg of KO^{t}Bu was added and the reaction was continued until the complete disappearance of the spot of lower R_f (6 h). The crude reaction mixture was poured onto water, extracted with EtOAc, the extract was dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (1:1, hexanes/EtOAc) gave allenamide **3d** as an amorphous solid (1.21 g, 74%). ^{1}H NMR (δ ppm): (mixture of a major and minor rotamers) 7.86 (d, $J = 7.6$ Hz, H_M), 7.81 (d, $J = 7.6$ Hz, H_m), 7.67 (t, $J = 6.5$ Hz, H_m, C=C=CH), 7.42 (t, $J = 7.6$ Hz, H_M), 7.28 (t, $J = 7.6$ Hz, H_m), 7.21–7.03 (m, $2H_M$+$2H_m$), 6.86–6.82 (m, $2H_M$), 6.74–6.69 (m, H_M+H_m), 6.47 (d, $J = 8.1$ Hz, H_m), 6.33–6.29 (m, H_M+H_m), 5.54 (t, $J = 6.2$ Hz, $2H_m$, CH_2=C=C), 5.40 (br s, $2H_M$, CH_2=C=C), 3.89 (s, $3H_M$, CH_3O), 3.87 (s, $3H_M$, CH_3O), 3.84 (s, $3H_m$, CH_3O), 3.73 (s, $3H_m$, CH_3O), 4.1–3.7 (br m, H_M+$2H_m$), 3.51 (br m, H_m), 3.36 (br m, H_m), 2.98 (br m, $2H_M$), 2.75 (t, $J = 7.4$ Hz, H_M). ^{13}C NMR (δ ppm) 202.8 (C=C=C), 200.3 (C=C=C), 168.7 (C=O), 168.2 (C=O), 149.0 (C), 148.9 (C), 147.8 (C), 147.6 (C), 141.3 (C), 141.1 (C), 139.4 (CH), 138.9 (CH), 131.3 (C), 131.0 (CH), 130.5 (C), 130.2 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 120.9 (CH), 120.8 (CH), 112.2 (CH), 111.9 (CH), 111.2 (2 × CH), 101.1 (CH), 97.5 (CH), 92.7 (C), 92.4 (C), 87.1 (CH_2), 87.0 (CH_2), 55.9 (CH_3O), 55.9 (CH_3O), 55.9 (CH_3O), 55.7 (CH_3O), 49.2 (CH_2), 45.5 (CH_2), 33.9 (CH_2), 32.7 (CH_2). IR (film, cm^{-1}): 3049, 2940, 2833, 2359, 1647,1514.
9. All new compounds were fully characterized spectroscopically and had satisfactory elemental analyses or HRMS data.
10. *Typical procedure for cyclization of allenamides*: TFA (17 μL) was added to a solution of allenamide **3d** (600 mg, 1.34 mmol) in 40 mL of dry dichloromethane, and the mixture was stirred at room temperature for 24 h. Extra TFA (20 μL) was added, and stirring was continued for a further 5 days. The reaction mixture was then washed with $NaHCO_3$ and water, and the organic solvent dried and evaporated. Purification by flash chromatography on silica gel (1:1 hexanes/EtOAc) gave isoquinoline **5d** as a foam (470 mg, 78%). ^{1}H NMR (δ ppm): (mixture of a major and minor rotamers) 7.85 (d, $J = 7.8$ Hz, H_M), 7.80 (d, $J = 6.9$ Hz, H_m), 7.41 (m, H_M+H_m), 7.34–7.20 (m), 7.15 (m, H_M+H_m), 6.69 (s, H_M+H_m), 6.62 (s, H_M), 6.45 (s, H_m), 6.26–6.00 (m, H_M+$2H_m$), 5.93–5.80 (m, H_m), 5.36–5.14 (m), 5.00–4.78 (m), 3.90 (s, $3H_M$+$3H_m$, 2 × CH_3O), 3.89 (s, $3H_M$, CH_3O), 3.82 (s, $3H_m$, CH_3O), 3.81 (m, H_m), 3.61–3.11 (m), 2.87–2.57 (m). MS (*m*/*e* %): 449 (M^+, 3), 322 (M^+−I, 100), 231 (92).
11. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
12. Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117.
13. Frisch, M. J. et al. GAUSSIAN03, *Revision B. 05*; Gaussian: Wallingford, CT, 2004.
14. For proper computation of thermochemical properties, free rotors should be considered explicitly. The entropy penalty should therefore be higher than was computed with the harmonic approximation used here.
15. For a recent synthesis of protoberberines, see: Orito, K.; Satoh, Y.; Nishizawa, H.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 2535.
16. *Procedure for the synthesis of* **6d**: $Pd(OAc)_2$ (4 mg, 0.02 mmol), Et_4NBr (35 mg, 0.17 mmol) and K_2CO_3 (58 mg, 0.43 mmol) were successively added to a solution of vinylisoquinoline **5d** (75 mg, 0.17 mmol) in 3 mL of dry DMF. The mixture was heated under Ar at 100 °C for 10 h, and then cooled down, poured onto water and extracted with EtOAc. The organic extract was dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (6:4 hexanes/EtOAc) gave protoberberine **6d** as an amorphous solid (38 mg, 70%). ^{1}H NMR (δ ppm): 8.14 (d, $J = 7.1$ Hz, 1H, Ar–H), 7.64–7.38 (m, 3H, Ar–H), 6.71 (s, 1H, Ar–H), 6.66 (s, 1H, Ar–H), 5.76 (s, 1H, C=CH), 5.43 (s, 1H, C=CH), 5.14 (s, 1H, CHN), 5.02–4.88 (m, 1H, CH_2), 3.86 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 3.20–3.03 (m, 2H, CH_2), 2.82–2.67 (m, 1H, CH_2). ^{13}C NMR (δ ppm): 163.8 (C=O), 148.1 (C), 146.9 (C), 140.2 (C), 136.1 (C), 132.0 (CH), 128.7 (CH), 128.7 (CH), 128.2 (CH), 127.9 (C), 127.3 (C), 125.5 (C), 123.6 (CH), 115.1 (CH_2), 111.7 (CH), 109.5 (CH), 61.0 (CH), 55.9 (CH_3O), 55.8 (CH_3O), 41.3 (CH_2), 27.7 (CH_2). MS (*m*/*e* %): 321 (100), 320 (38), 290 (60). IR (film cm^{-1}): 2937, 2833, 1650, 1641, 1514. Elem. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.47; H, 6.12; N, 4.09.
17. We also tried the cyclization under standard tin-mediated radical conditions. Since amide **5d** exists in solution as a mixture of rotamers, the carbonyl group was first reduced with AlH_3/THF. However, treatment of the resulting vinylisoquinoline with Bu_3SnH/AIBN afforded only polymerization products.