Tetrahedron Letters 55 (2014) 2446–2449

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

6π/10π-Electrocyclization of ketene-iminium salts for the synthesis of substituted naphthylamines

Emmanuelle Villedieu-Percheron [a], Saron Catak [b], Didier Zurwerra [a], Roman Staiger [a], Mathilde Lachia [a], Alain De Mesmaeker [a,*]

[a] Syngenta Crop Protection AG, Crop Protection Research, Research Chemistry, Schaffhauserstrasse 101, CH-4332 Stein, Switzerland
[b] Bogazici University, Chemistry Department, Bebek, 34342 Istanbul, Turkey

ARTICLE INFO

Article history:
Received 24 January 2014
Revised 20 February 2014
Accepted 28 February 2014
Available online 11 March 2014

Keywords:
Electrocyclization
Ketene-iminium salts
Naphthylamines
DFT

ABSTRACT

An intramolecular 6π/10π-electrocyclization from ketene-iminium salts was developed for the preparation of naphthylamines. Various substituents on the nitrogen, on the aromatic ring, and on the olefin were studied. Tricyclic skeletons were obtained in few steps and good overall yields. The electrocyclization of ketene-iminium salts has been computationally explored by means of DFT calculations and their activation barriers were compared to the parent triene as well as the corresponding dienyl allenes and dienyl ketenes. Electrocyclizations for ketene-iminium salts were shown to be highly exergonic and have much smaller barriers to activation.

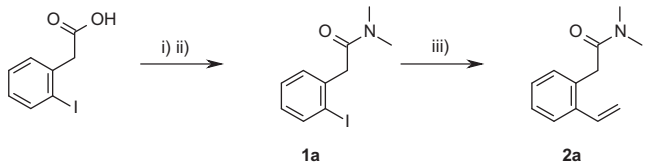
Aromatic amines are very important structural motifs and building blocks which have attracted considerable attention. As a consequence, various methodologies to access substituted aromatic amines have been reported and for example Buchwald–Hartwig amination has been frequently used.[1] This method is accelerated by electron-withdrawing groups on the aromatic halide and by highly nucleophilic amines. However, acyclic secondary amines as well as electron-rich or -neutral aryl halides are less favorable substrates for this methodology. Electrocyclization has been reported as a powerful tool for the synthesis of complex structural motifs. These intramolecular reactions have been investigated for trienes and for their corresponding imines,[2] dienyl allenes,[3] dienyl ketenes,[4] and dienyl keteneimines,[5] leading to ring closure products which in some cases could be transformed into aromatic skeletons. The thermal transformation of hexa-1,3,5-triene into cyclohexa-1,3-diene has limited use owing to the high temperatures required for this transformation. However, changing the hybridization of a bonding atom from sp^2 to sp (as in the case of dienyl allenes and dienyl ketenes) lowers E_a by 15–20 kcal mol^{-1}.[6] Ketene-iminium salts have been developed as an improved alternative to ketene for intra- and intermolecular [2+2] cycloaddition reactions. These charged species increase very significantly the electrophilicity of the central sp carbon in the ketene-iminium salts, promoting the attack of a nucleophile.[7] Moreover, ketene-iminium salts do not polymerize, are easily accessible from amides, and are currently useful tools for selectivity and stereocontrol in [2+2] cycloadditions.[8] However, to the best of our knowledge, the use of vinyl ketene-iminium salts in 6π/10π-electrocyclization has never been reported. We describe herein the first example of such an electrocyclization reaction which leads to substituted naphthylamines carrying even sterically demanding residues which are difficult to access with the usual Buchwald–Hartwig coupling.[9]

The conditions of the reaction were first optimized with *N*,*N*-dimethyl-2-(2-vinylphenyl)acetamide **2a**. This product was obtained in good yield via a two-step synthesis from commercially available 2-iodophenylacetic acid. This was converted to the corresponding acyl chloride which on treatment with *N*,*N*-dimethylamine provided the corresponding amide **1a**. Subsequent Stille coupling with tributylvinyltin gave vinylamide **2a** in very good yield (Scheme 1).

In a first attempt to generate the ketene-iminium salt, we used the standard conditions already described for intramolecular [2+2] cycloadditions.[10] Thus, amide **2a** was treated with 1.1 equivalent of triflic anhydride and 2,4,6-trimethylpyridine (*sym*-collidine) in dichloromethane. To our delight, naphthylamine **3a** was isolated in 48% yield (Scheme 2, Table 1). In order to optimize the conditions, the amount of *sym*-collidine, the concentration, the solvent, and the temperature of the reaction were studied. The yield was ncreased to 60% using 2.4 equiv of *sym*-collidine, 1.1 equiv of Tf_2O, in a 0.05 M solution in CH_2Cl_2, at 40 °C. The importance of the concentration was investigated with no significant effect

* Corresponding author. Tel.: +41 62 8660268; fax: +41 61 3238726.
E-mail address: alain.de_mesmaeker@syngenta.com (A. De Mesmaeker).

http://dx.doi.org/10.1016/j.tetlet.2014.02.135
0040-4039/



Scheme 1. Preparation of *N*,*N*-dimethyl-2-(2-vinylphenyl)acetamide **2**. Reagents and conditions: (i) oxalyl chloride (2 equiv), DMF (cat.), CH_2Cl_2; (ii) $NHMe_2$ (4 equiv), CH_2Cl_2, 0 °C, 99%; (iii) vinylstannane (1.5 equiv), $Pd(PPh_3)_4$ (3 %), toluene, reflux, 16 h, 84%.

on the yield of **3a**, as expected for ketene-iminium chemistry (entry 3).

Higher amounts of *sym*-collidine were detrimental (entry 4). Stirring in dichloromethane between ambient temperature and reflux gave the best results. When the reaction was carried out below room temperature or above 40 °C, decomposition occurred (entries 5, 8 and 10). The use of 2,6-ditertbutyl-4-methylpyridine did not improve the yield (Entry 7). When the reaction was carried out in the dark, the naphthalene derivative **3a** was obtained in similar yield (entry 9). Changing the solvent to acetonitrile did not lead to any further improvements (entry 11).

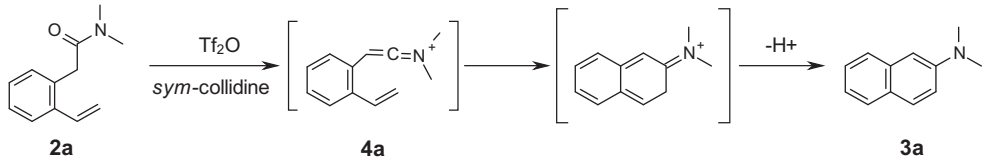
Having established suitable reaction conditions, we then focused on the scope by varying substituents (R_1, R_2) on the amide **2a**–**h** (Table 2), on the aromatic ring (R_3) **2i**–**k** (Table 3) and on the vinyl group (R_4, R_5) **2l**–**q** (Table 4).

We started by varying the amide moiety (Table 2). Linear and cyclic alkyl chains were chosen, as well as aryl substituents which would lead to more or less hindered and/or electrophilic ketene-iminium intermediates. These amides **2a**–**h** were prepared according to the previously described two-step synthesis (Scheme 1).

Table 2 describes the first set of different naphthalene derivatives obtained by using 2.4 equiv of *sym*-collidine, 1.1 equiv of triflic acid, in dichloromethane (0.05 M) at 40 °C. For some of these reactions, 1.8 equiv of Tf_2O were necessary to reach full conversion. Increasing the amount or triflic acid led to decomposition. Moreover, product **3g** was obtained by conducting the reaction at room temperature. Once again, higher temperatures led to decomposition and loss of material. Some of these products were found to be light sensitive and all the manipulations (including workup, purification, and evaporation) were carried out in the dark.[11] The reaction tolerates a large variety of amides; even hindered nitrogen substituents gave good results. However, the morpholine derivative **3f** was isolated in low yield. Even an increase in temperature to 60 °C did not lead to full conversion. Side-product formation was observed during the reaction which led to a lower yield of isolated product **3f**. In this particular case, the product itself could be reactive toward ketene-iminium salt due to the nucleophilic oxygen atom of the morpholine ring, leading to loss of material.

We then focused on the influence of different substituents on the aromatic ring to the outcome of the 6π/10π-electrocyclization (Table 3). Full conversion was realized with 1.8 equiv of Tf_2O under reflux, although 1.5 equiv were sufficient at room temperature. Table 3 describes the results obtained for various derivatives. Yields decreased when the reaction was carried out under reflux, probably due to the degradation of the products under the reaction conditions. Working at room temperature improved the results with completion after 10 min. For example the product **3j** where R_3 = OMe was rather unstable in the reaction mixture.

We then turned our attention to the influence of substituents on the olefin. Table 4 summarizes the effect of varying substituents R_4 and R_5 on the olefin part on the reaction outcome. Compound **3l** was isolated in 60% yield despite its light sensitivity. Interestingly, the tricyclic naphthylamines **3m**–**o** were isolated in better yields although the steric hindrance at the extremity of the double bond could have decreased the reactivity of such reagents. The tricyclic structures of the products **3m**–**o** do not allow the coplanar orientation of the amine and of the adjacent aromatic ring due to steric repulsion between the saturated ring and the *N*,*N*-diisopropyl moiety. Consequently, the derivatives **3m**–**o** were less light sensitive than the other products we have described previously. These types of structures **3m**–**o** are so far difficult to access by other methodologies.[12] Electron-donating groups were introduced on both positions of the double bond. Whereas **3p** (R_4 = OEt, R_5 = H) was obtained in very good yield, compound **3q** (R_4 = H, R_5 = OEt) could not be obtained at all. In the latter case, only starting material was



Scheme 2. Electrocyclization of ketene-iminium salt **4a** to naphthylamine **3a**.

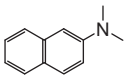
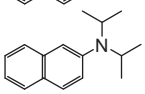
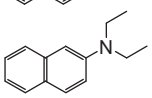
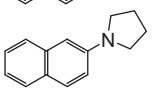
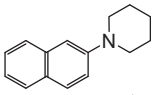
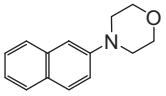
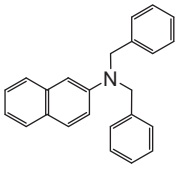
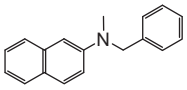
Table 1
Optimization of the condition for electrocyclization of amide **2a** to naphthylamine **3a**

Entry	*sym*-Collidine (equiv)	Triflic anhydride (equiv)	Concentration of **2a** (mol L^{-1})	Solvent	*T* (°C)	Yield (%)
1	1.2	1.1	0.05	CH_2Cl_2	rt	48
2	2.4	1.1	0.05	CH_2Cl_2	rt	58
3	2.4	1.1	0.02	CH_2Cl_2	rt	54
4	5	1.1	0.05	CH_2Cl_2	rt	44
5	2.4	1.1	0.05	CH_2Cl_2	0	23
6	2.4	1.1	0.05	CH_2Cl_2	40	58
7	2.4[a]	1.1	0.05	CH_2Cl_2	rt	0
8	2.4	1.1	0.05	$(CH_2)_2Cl_2$	80	39
9[b]	2.4	1.1	0.05	CH_2Cl_2	40	60
10[b]	2.4	1.1	0.05	$CHCl_3$	60	Traces
11	2.4	1.1	0.05	MeCN	40	35

[a] 2,6-Diterbutyl-4-methylpyridine.
[b] The reaction was carried out in the dark.

Table 2
Effect of the nitrogen substituents on the electrocyclization reaction

2a-h **3a-h**

Entry	Product	Yield
1		60% (**3a**)
2		83% (**3b**)
3		58%[a] (**3c**)
4		50%[a] (**3d**)
5		65%[a] (**3e**)
6		28% (**3f**)
7		48% [a,b] (**3g**)
8		54%[a] (**3h**)

General conditions: 1.1 equiv of Tf_2O, 2.4 equiv of collidine, dichloromethane, 0.05 M, reflux.
[a] 1.8 equiv of Tf_2O and 3.0 equiv of collidine were added to reach completion.
[b] Reaction carried out at rt.

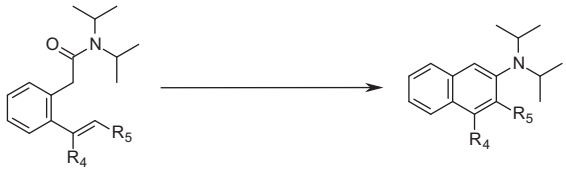
Table 3
Effect of the substituents on the aromatic ring on the electrocyclization reaction

2i-k **3i-k**

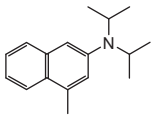
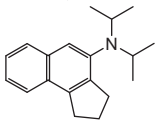
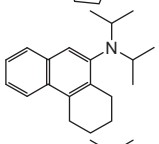
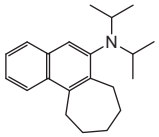
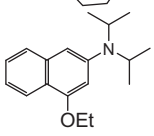
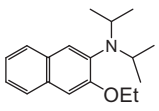
Entry	R^3	Yield at rt (%)	Yield at reflux (%)
1	Cl	78 (**3i**)	66
2	OMe	56 (**3j**)	41
3	Me	71 (**3k**)	62

General conditions: 3.0 equiv of *sym*-collidine, 1.8 equiv of Tf_2O, dichloromethane 0.05 M.

Table 4
Effect of the substituents on the vinyl group on the electrocyclization reaction



2l-q **3l-q**

Entry	Product	Yield
1		60% (**3l**)
2		73% (**3m**)
3		86% (**3n**)
4		75% (**3o**)
5		86% (**3p**)
6		0% (**3q**) (**2q**: E)

General conditions: 3.0 equiv of *sym*-collidine, 2.0 equiv of Tf_2O, dichloromethane, 0.05 M, reflux.

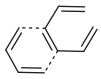
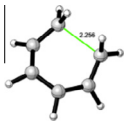
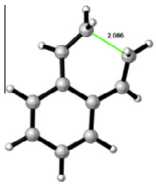
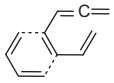
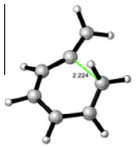
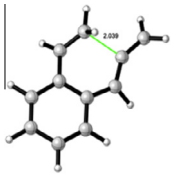
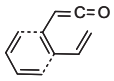
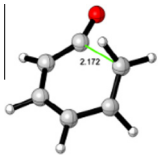
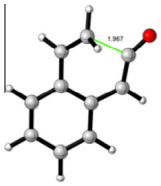
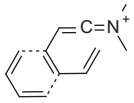
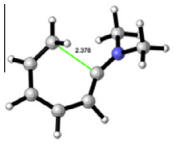
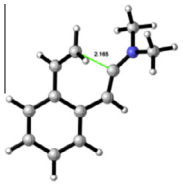
recovered. In **3p**, the reactivity was probably enhanced by increasing the HOMO coefficient in the β-position (R_5), leading to a better nucleophilic attack of the double bond to the ketene-iminium salt. The lack of reaction in the case of **3q** is most likely due to steric clash between the ethoxy and isopropyl moieties, disfavoring the interaction between the central carbon atom of the ketene-iminium salt and the terminal carbon atom of the olefin. The influence of an additional substituent at the benzylic position adjacent to the amide will be investigated in a near future.

A DFT study was performed to compare the electrocyclization among the parent triene system, the corresponding dienyl allenes, dienyl ketenes, and dienyl ketene-iminiums. The electrocyclization reactions were modeled in gas-phase using M06-2X,[13] a *meta*-GGA known to perform well in organic systems with dispersion effects.[14] Geometry optimizations and frequency calculations were performed using the Gaussian 09 program package.[15] Thermal corrections were obtained from vibrational frequencies, which were also used to confirm the nature of the stationary points. Free energy corrections are reported at 1 atm and 298 K.

From the calculated data shown in Table 5, it is clear—both kinetically and thermodynamically—that ketene-iminium salts (row 4) will undergo electrocyclization reactions more easily; ketene iminiums are followed by ketenes, allenes, and finally, trienes. In the extended systems, the evolution of bond distances within the aromatic rings reveals that all π electrons are involved in the process, hence indicating a 10π electrocyclization.

In summary, we have disclosed herein the first example of an efficient 6π/10π-electrocyclization reaction of ketene-iminium salts to form naphthylamines.[12] A variety of substituents on the

Table 5
Transition state structures, relative free energy barriers ($\Delta G^{\ddagger}$), and reaction free energies (ΔG_{rxn}) for 6π/10π electrocyclizations[a]

Substrate	Transition state structure	$\Delta G^{\ddagger}$ ΔG_{rxn}	Transition state structure	$\Delta G^{\ddagger}$ ΔG_{rxn}
		30.9[b] -14.2		39.7 3.4
		21.1 −28.9		23.5 −13.6
		14.9 −23.8		18.7 −7.0
		8.5 −44.5		6.4 −35.4

[a] M06-2X/6-31+G(d,p); free energies in kcal/mol; critical distances in Å.
[b] Experimental activation energy for the 6π electrocyclization of hexa-1,3,5- triene: 29.9 ± 0.5 kcal/mol.[16]

nitrogen atom, on the aromatic ring, and on the vinyl group have been investigated, leading to the formation of the corresponding naphthylamines. The reaction tolerates a large scope of functionalities, from acyclic to cyclic, hindered or unhindered, electron-rich and electron-poor substituents, and allowed fast access to structurally more complex tricyclic structures which would be difficult to obtain otherwise. The extension of this methodology to further various aromatic amine derivatives as well as other scaffolds is ongoing and will be reported soon.

References and notes

1. (a) Raders, S. M.; Moore, J. N.; Parks, J. K.; Miller, A. D.; Leißing, T. M.; Kelley, S. P.; Rogers, R. D.; Shaughnessy, K. H. *J. Org. Chem.* **2013**, *78*, 4649–4664; (b) Yamasaki, R.; Ikeda, H.; Masu, H.; Azumaya, I.; Saito, S. *Tetrahedron* **2012**, *68*, 8450–8456; (c) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049–11061; (d) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505–3508.
2. (a) Jutz, C.; Wagner, R. M. *Angew. Chem., Int. Ed.* **1972**, *11*, 315–318; (b) Kobayashi, T.; Sakaguchi, T.; Katsumura, S. *Heterocycles* **2013**, *87*, 729–761; (c) Souto, J. A.; Perez, M.; Lopez, C. S.; Alvarez, R.; Torrado, A.; de Lera, A. R. *J. Org. Chem.* **2010**, *75*, 4453–4462.
3. Okamura, W. O.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034–1041.
4. (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672–1674; (b) Liebeskind, L. S.; Jewell, S. I. C. F. *J. Org. Chem.* **1986**, *51*, 3065–3067; (c) Barron, C. A.; Khan, N.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 1728–1730; (d) Brenna, E.; Fuganti, C.; Perozzo, V.; Serra, S. *Tetrahedron* **1997**, *53*, 15029–15040; (e) Myers, A. G.; Horiguchi, Y. *Tetrahedron Lett.* **1997**, *38*, 4363–4366; (f) Brenna, E.; Fuganti, C.; Fronza, G.; Gatti, F. G.; Sala, F.; Serra, S. *Tetrahedron* **2007**, *63*, 2351–2356; (g) Alajarin, M.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A.; Bautista, D. *Org. Lett.* **2005**, *7*, 5281–5284; (h) Alajarin, M.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A. *J. Org. Chem.* **2006**, *71*, 8126–8139; (i) Zografos, A. L.; Mitsos, C. A.; Igglessis-Markopoulou, O. *J. Org. Chem.* **2001**, *66*, 4413–4415.
5. (a) Alajarin, M.; Marin-Luma, M.; Vidal, A. *Eur. J. Org. Chem.* **2012**, 5637–5653; For a tandem 1,5-hydrid shift/6π electrocyclization of ketene-imines see: (b) Alajarin, M.; Bonillo, B.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A. *Eur. J. Org. Chem.* **2011**, 1896–1913.
6. Schmidt Burnier, J.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001–3020.
7. (a) Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* **1972**, *94*, 2870–2872; (b) Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed.* **1981**, *20*, 879–880; (c) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793–811.
8. Madelaine, C.; Valerio, V.; Maulide, N. *Chem. Asian J.* **2011**, *6*, 2224–2239.
9. For the benzannulation from alkynes and amines leading to 2-aminonaphthalenes see Jin, T.; Yang, F.; Yamamoto, Y. *Org. Lett.* **2010**, *12*, 388–390.
10. (a) Lachia, M.; Jung, P. M. J.; De Mesmaeker, A. *Tetrahedron Lett.* **2012**, *53*, 4514–4517; The use of 2-fluoropyridine to improve the yield of ketene-iminium formation and reaction has been reported recently and could be beneficial for the present process see: (b) Peng, B.; Geerdink, D.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 14968–16971.
11. For example, studies on *N*-phenyl-1-naphthylamine for photodegradation yielded a half-life in water of 5.7 min. See International program on chemical safety; concise international chemical assessment document n°9, World Health Organization, Geneva, 1998.
12. *Typical procedure for the 6π/10π-electrocyclization reaction*: To a solution of amide **2o** (104 mg, 0.33 mmol) in dry dichloromethane (7 mL) was added *sym*-collidine (0.133 mL, 0.995 mmol) followed by a solution of triflic anhydride (0.116 mL, 0.663 mmol) in 0.3 mL of dichloromethane giving a red solution. The solution was stirred at 40 °C for 45 min. The reaction mixture was cooled to room temperature and then treated with $NaHCO_3$ (satd aq). The aqueous layer was extracted with dichloromethane and the combined organic layers were dried and concentrated. Purification by flash chromatography (cyclohexane/EtOAc 5:1) afforded the desired product **3o** (73 mg, 75%) as a pale-yellow oil. ES: 296 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12 (1H, d, J = 8.0 Hz), 7.78 (1H, d, J = 7.5 Hz), 7.58 (1H, s), 7.32–7.51 (2H, m), 3.56–3.70 (2H, m), 3.35–3.45 (2H, m), 3.26–3.34 (2H, m), 1.83–1.95 (2H, m), 1.70–1.80 (2H, m), 1.56–1.66 (2H, m), 1.06 (6H, d, J = 6.5 Hz), 1.00 (6H, d, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.7, 144.5, 139.0, 132.3, 129.7, 128.2, 125.6, 124.9, 124.2, 123.2, 50.1, 32.0, 28.8, 28.2, 27.1, 26.7, 21.8, 20.4.
13. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
14. (a) Winne, J. M.; Catak, S.; Waroquier, M.; Van Speybroeck, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 11990–11993; (b) Catak, S.; Hemelsoet, K.; Hermosilla, L.; Waroquier, M.; Van Speybroeck, V. *Chem. Eur. J.* **2011**, *17*, 12027–12036.
15. Gaussian 09, Revision C.01, M. J. Frisch et al., Gaussian Inc., Wallingford: CT, 2009.
16. Marvell, E. N.; Caple, G.; Schatz, B. *Tetrahedron Lett.* **1965**, *6*, 385–389.