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LETTERS

Competitive fine-tuning of heteroaromatic imines as dienophiles or dienes in the Lewis acid-mediated Diels–Alder reaction with cyclopentadiene

Teck-Peng Loh,* Kevin Siong-Ve Koh, Keng-Yeow Sim and Weng-Kee Leong
Department of Chemistry, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260, Singapore

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Abstract

Heteroaromatic imines function as dienophiles or dienes in the Lewis acid-mediated Diels–Alder reaction with cyclopentadiene depending on the substituent on the imine. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: aza Diels–Alder; imine; azadiene.

The aza Diels–Alder reaction is one of the most useful reactions for the synthesis of alkaloids.[1–4] Although the Lewis acid-catalyzed aza Diels–Alder reaction has been carried out successfully using various dienes and imines, the reactions of cyclic dienes with de-activated imines have been less successful.[5–7] Most recently, Wang found that lanthanide triflates were excellent catalysts for the aza Diels–Alder reaction of various dienes with aliphatic imines but gave significantly lower yields (about 8–12%) with aromatic imines.[7] In particular, the three component system of benzaldehyde, benzylammonium chloride and cyclopentadiene catalyzed by lanthanides and transition metals has been reported to give the products in very low yields. Our interest in azabicyclo[2.2.1.]heptene derivatives as analogues of epibatidine[8] has prompted us to develop a new method for the aza Diels–Alder reaction of cyclopentadiene with 3-pyridinecarboxaldehyde derived imines (Scheme 1). In this paper, we demonstrate that an imine can function as a dienophile or an azadiene depending on the choice of the substitutent on the imine (Scheme 1).

Model studies were based on 3-pyridinecarboxaldehyde as this offers a very short route to the formation of epibatidine analogues. The results are summarized in Table 1. Our efforts in forming these analogues with various Lewis acids like $Yb(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_2$, $Sn(OTf)_2$, $ZnCl_2$, $ZnCl_2/ZnO$ for the aza Diels–Alder reaction under aqueous or anhydrous conditions using 3-pyridinecarboxaldehyde gave the desired products in low yield. On the other hand, the use of stronger Lewis acids such as $EtAlCl_2$, $TiCl_4$, BBr_3, $BF_3 \cdot Et_2O$, $SnCl_4$, and $SnCl_2$ under anhydrous conditions mainly caused premature

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* Corresponding author.

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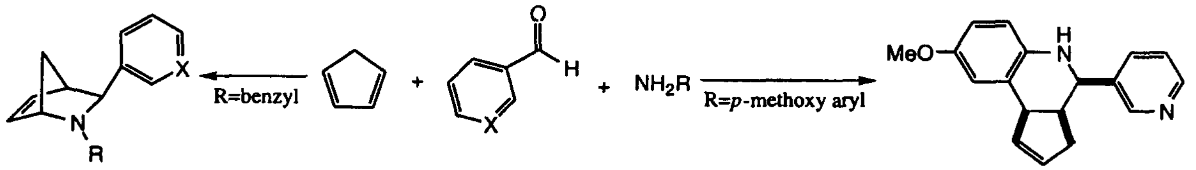
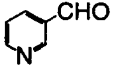
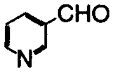
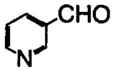
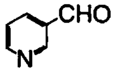
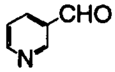
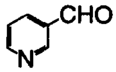
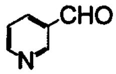
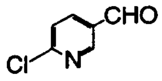


Scheme 1.

Table 1

Aza Diels–Alder reaction of various heteroaromatic and various imines with cyclopentadiene

Entry	Aldehyde	Primary Amine or Ammonium Chloride Salt	Conditions	Yield[b] (%)
1		Benzylammonium chloride	10 mol% $Yb(OTf)_3.3H_2O$,)))), H_2O	5
2		Benzylammonium chloride	10 mol% $InCl_3.3H_2O$,)))), H_2O,	8
3		Benzylammonium chloride	$AlCl_3$,)))), CH_2Cl_2	18
4		Benzylammonium chloride	Method A	25
5		Benzylamine	Method B	41
6		*S*-α-methylbenzylamine	Method B	53
7		*R*-α-methylbenzylamine	Method B	48[c]
8	 1	*S*-α-methylbenzylamine	Method B	28 (9)[d]

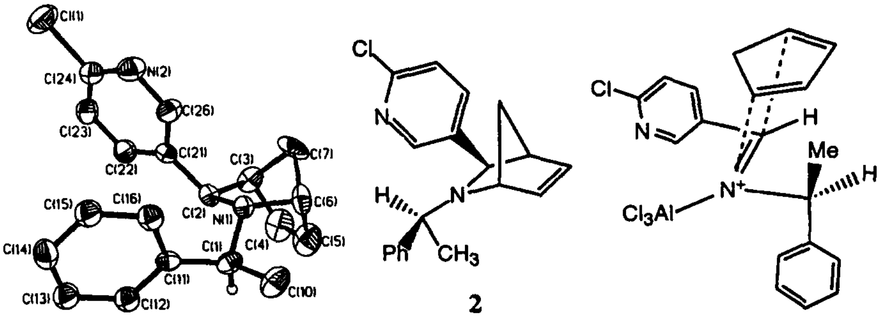
[a] All reactions were carried out under anhydrous conditions. [b] Isolated yield. [c] Use of commercially available *R*-α-methylbenzylamine (95%) resulted in the lower yield. [d] Unidentified side product with α-methylbenzyl group cleaved.

dimerization and polymerization of cyclopentadiene. We tried the three component reaction (method A) as demonstrated by Grieco[9] and Wang[7] as well as using the preformed imine with various Lewis acids and organic (e.g. triflic acid, CF_3COOH) or mineral acids but were unsuccessful until we chanced upon $AlCl_3$ moderated with triethylamine (method B) both under sonication and shaking under anhydrous conditions at 0°C. Reactions using the preformed imine (method B) gave the products in better yields compared to the reaction carried out without using preformed imine (method A) (entries 4 and 5).

Sonication and shaking was neccessary due to the relative insolubility of $AlCl_3$ with moderation using 1/3 molar equivalence of Et_3N (an equimolar amount of the latter amine merely deactivated the Lewis acid). The Et_3N also served to enhance the solubility of the Lewis acid. The use of an equimolar amount of saturated $AlCl_3$ in dichloromethane involved a much larger volume of solvent and gave rise to a high degree of cyclopentadiene polymerization and lower yields. In the absence of sonication much lower yields were observed. Substitution of $AlCl_3$ with $EtAlCl_2$, whether in catalytic or equimolar amounts gave distinctively lower yields under the conditions of method B. The low temperature helps to minimize the dimerization and polymerization of cyclopentadiene. However, multiple sequential addition of cyclopentadiene did not improve the overall yield.

Once the reaction was optimized, *S*-α-methylbenzylamine was used with both 3-pyridinecarboxyaldehyde and 6-chloro-3-pyridinecarboxyaldehyde (**1**)[10] to afford the bicyclic adduct (**2**) (28% yield), the latter with significant (98:2) diastereoselectivity; a side-reaction giving an as yet unidentified debenzylated adduct (Table 1, entry 8). The absolute stereochemistry of the chiral *exo*-product (**2**) 2-*S*-α-methylbenzylaza-3-(6′-chloro-3′-pyridyl)-5,6-bicyclo[2.2.1]heptene was confirmed by X-ray crystallography using the chiral auxiliary as a reference.

The $AlCl_3$ probably promotes the formation of the iminium ion intermediate and polarization of the imine bond hence decreases the LUMO of this dienophile which synergistically results in slightly greater reactivity. This observed absolute stereochemistry according to the X-ray structure reflects the possible $AlCl_3$-transition state as shown in Scheme 2.



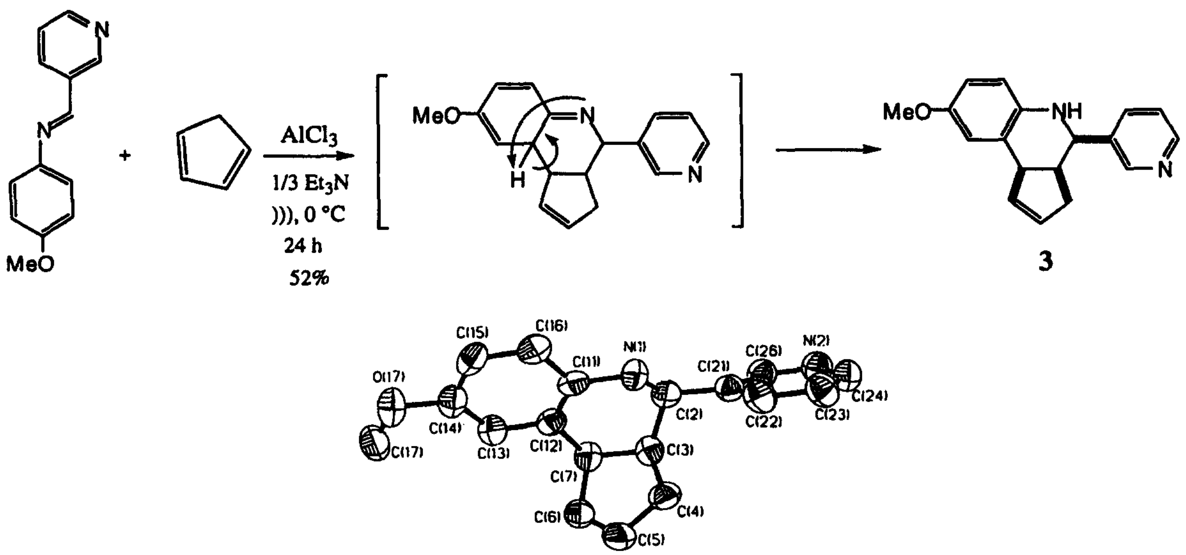
Scheme 2.

One curious but not entirely unexpected result was from the Diels–Alder reaction using the imine derived from *p*-anisidine. From the X-ray diffraction analysis of the product, the bicyclo[2.2.1]heptene structure was not obtained. Instead, another hetero Diels–Alder reaction had occurred utilizing the imine as the azadiene and the cyclopentadiene as dienophile to afford the quinoline **3** with the relative stereochemistry as shown in Scheme 3.[11–14]

In conclusion, we have demonstrated the efficacy of an $AlCl_3$–1/3Et_3N complex for use in the mediation of aza Diels–Alder reactions between deactivated heteroaromatic imines and cyclopentadiene towards the formation of aza-3-(3′-pyridyl or aromatic)-5,6-bicyclo[2.2.1]heptene-type systems. Unique reactivities of imines which work as both dienophiles and azadienes have been revealed. The use of this three component synthesis for the construction of a library of this class of compounds for biological evaluation is now in progress.

1. Experimental procedure

Typically a preformed suspension of $AlCl_3$ (2.54 g, 0.019 mol) and triethylamine (0.88 mL, 0.0063 mol) in dry CH_2Cl_2 (20 mL) was added to a cooled (−78°C) solution of 2-aza-3-phenyl-1-(3-pyridyl)prop-1-ene (3.72 g, 0.019 mol), and excess cyclopentadiene (4 mL) in CH_2Cl_2 (10 mL) with stirring over 5 min. The stirrer was removed and the RBF afixed onto a shaker and placed in a sonicating bath cooled to 0–5°C. This reaction was shaken and sonicated for 2–3 days. Workup comprised shaking with NaOH (10%, 30 mL) and extraction of the mixture with $CHCl_3$ (3×40 mL). The organic layer was dried with sodium sulphate, filtered and concentrated. The residue was purified by flash chromatography



Scheme 3.

using silica gel neutralised with triethylamine using ethyl acetate:hexane (1:9) to give the 2-aza-2-benzyl-3-(3-pyridyl)-bicyclo[2.2.1]hept-5-ene as a yellow oil (2.04 g, 41%).[15]

Acknowledgements

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References

1. Holmes, A. B.; Hamley, P.; Helmchen, G.; Marshall, D. R.; Mackinnon, J. W. M.; Smith, D. F.; Ziller, J. W. *J. Chem. Soc., Chem. Commun.* **1992**, 787.
2. Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37.
3. Bailey, P. D.; Brown, G. R.; Kober, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry.* **1991**, *2*, 1263.
4. Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.
5. Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.
6. Pfrengle, W.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067.
7. Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 2169.
8. For a review, see: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179, and references cited therein.
9. Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.
10. 6-Chloro-3-pyridinecarboxyaldehyde (**1**) was derived from the reduction of 6-chloronicotinic acid with $LiAlH_4$ and the 6-chloro-3-pyridylcarbinol formed was oxidized to the corresponding aldehyde with PCC. Corey, E. J.; Loh, T. P.; AchyuthaRao, S.; Daley, D. C. and Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600.
11. Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Frisque-Hesbain, A. M.; Wynants, C. *Tetrahedron* **1995**, *51*, 11021, and references cited therein.
12. Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617, and references cited therein.
13. Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Paquette, L. A. Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp. 451, and references cited therein.
14. Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.

15. 2-Aza-2-benzyl-3-(3-pyridyl)-bicyclo[2.2.1]hept-5-ene R_f: 0.45 (1 ethyl acetate:2 hexane). FTIR (thin film): ν 3110.5, 3004.7, 1634.0 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (d, 1H, *J*=8.4 Hz), 1.69 (d, 1H, *J*=8.4 Hz), 2.75 (s, 1H), 2.90 (s, 1H), 3.38 (d, 1H, *J*=12.9 Hz), 3.52 (d, 1H, *J*=12.9 Hz), 3.83 (s, 1H), 6.25 (d, 1H, *J*=5.6 Hz), 6.61 (d, 1H, *J*=5.6 Hz), 7.18–7.31 (m, 5H), 7.35 (d, 1H, *J*=7.7 Hz), 7.84 (m, 1H), 8.41 (m, 1H), 8.73 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 44.3, 52.2; 57.8, 63.0, 64.9, 122.9, 126.7, 128.0, 128.8, 132.4, 135.0, 137.1, 139.1, 139.2, 147.4, 149.1. EIHRMS: calcd for $C_{18}H_{18}N_2$: 262.1470; found: 262.1482.