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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2365–2368

Lewis acid promoted aza Diels–Alder reactions of acyclic unactivated 5-dienyl pyrimidinones with *N*-arylimines: synthesis of novel quinoline derivatives

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Received 7 December 2006; revised 14 January 2007; accepted 24 January 2007
Available online 30 January 2007

Abstract—The chemo- as well as regioselective aza Diels–Alder reactions of 5-dienyl pyrimidinones with *N*-arylimines in the presence of a Lewis acid catalyst resulting in novel quinoline derivatives are reported.

The imino Diels–Alder reaction is a powerful synthetic tool for constructing nitrogen-containing six-membered heterocyclic compounds as well as for the synthesis of a variety of natural products.[1,2] The key to realizing this potential lies in the fact that the imine system needs to be activated or has to be used in conjunction with active dienes.[3] One of the most significant approaches in successfully accomplishing aza Diels–Alder cycloaddition reactions of *N*-arylimines involves the use of transition metals salts. A literature appraisal revealed the use of transition metal salts as catalysts in the aza Diels–Alder cycloaddition reactions of simple activated imines with unhindered activated alkenes, cyclopentadiene or symmetrical activated butadienes leading to the synthesis of tetrahydro/dihydroquinoline and di/tetrahydropyridine derivatives, respectively.[4] Such reactions in the presence of Lewis acid catalysts, however, were reported to suffer from disadvantages such as a lack of chemoselectivity, with imines acting both as dienophile as well as 2-azadiene resulting in the formation of a mixture of adducts and low isolated yields (17%).[5] To the best of our knowledge, there is no single report on Lewis acid catalysed DA reactions of 1-substituted unactivated butadienes with *N*-arylimines.

In view of the unique properties of Lewis acids in increasing the selectivity of reactions and as part of our continued interest in the synthesis of biologically important heterocycles,[6] it was thought worthwhile to compare the dienic properties of 5-dienyl-pyrimidinones in aza Diels–Alder reactions with *N*-arylimines. These reactions may lead to the synthesis of a variety of novel 5-substituted pyrimidinone derivatives, a number of which are known for their antitumour,[7] antiviral,[8] antitubercular,[9] antifungal,[10] molluscidal[11]and larvacidal[11] activity. Such compounds have shown activity against positive strand (vesicular stomatitis virus) RNA virus.[12]

The present Letter describes the chemo- as well as regioselective aza Diels–Alder cycloaddition reactions of *N*-arylimines (2-azadiene) with unactivated 1,3-butadiene tethered to a pyrimidinone ring[13] in the presence of different Lewis acids. Lewis acids such as magnesium(II) bromide, zinc(II) chloride, indium(III) chloride, yttrium triflate and scandium triflate were selected and examined for their effects on the chemo- and regioselectivities of the reactions. These reactions resulted in the formation of quinoline-substituted pyrimidinone derivatives **4** formed via oxidation of the initially formed intermediate **3** with the imine acting as a 2-azadiene, that is, the 4π component and the dienyl pyrimidinone as the 2π component.

The best results in term of yields and selectivity were obtained with magnesium(II) bromide (Scheme 1, Table 1, entries 1, 6 and 11) in the reactions of **1a**,**b** with imines **2a**–**c**. However, the reactions of **1a**–**c** with **2a**–**c** in the presence of yttrium triflate (Table 1, entries 4, 9 and 14), indium(III) chloride (Table 1 entries 3, 8 and 13) and scandium triflate (Table 1, entries 5, 10 and 15) in

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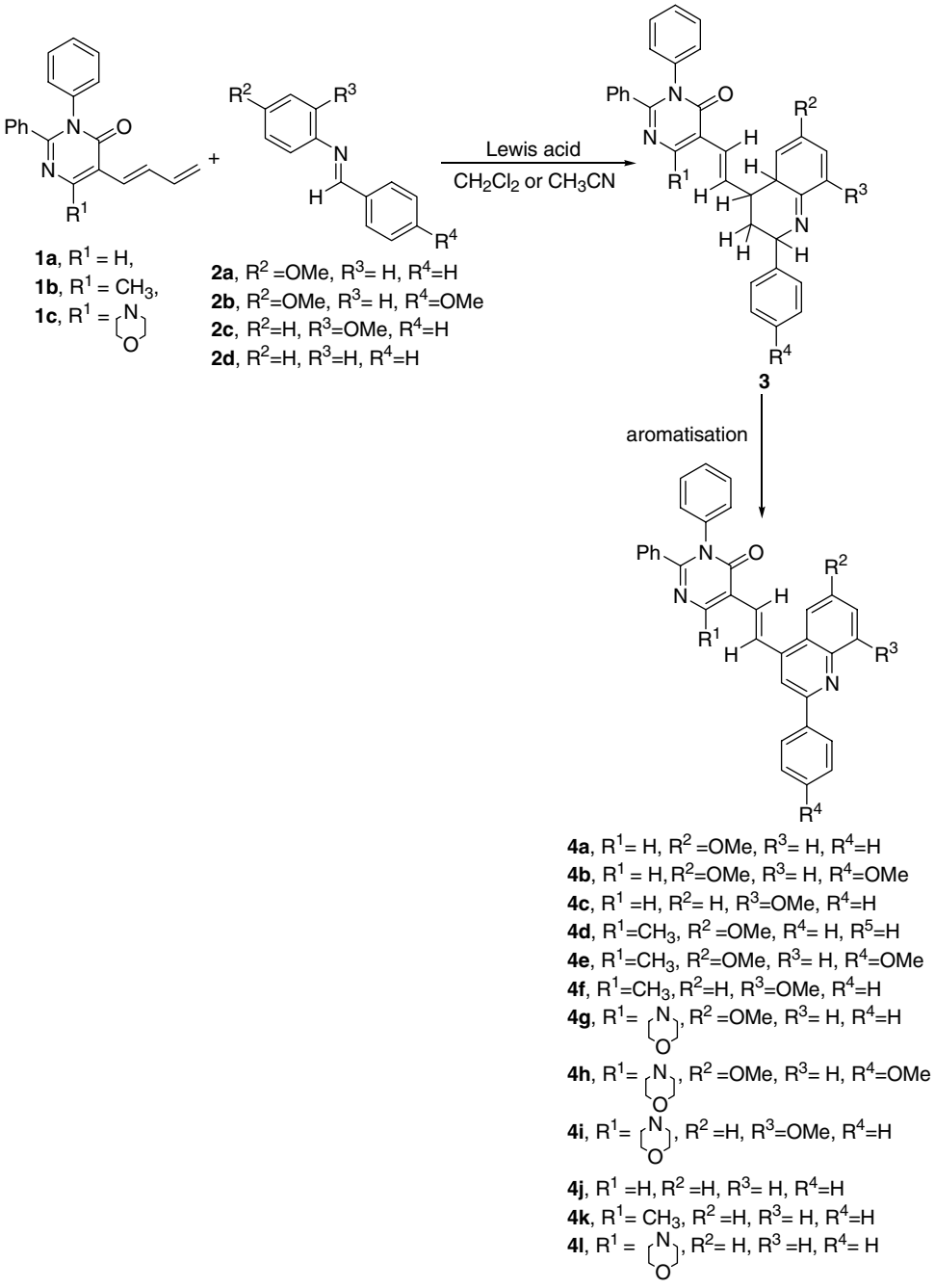
doi:10.1016/j.tetlet.2007.01.129



Scheme 1.

dry acetonitrile resulted in the formation of the corresponding cycloadducts in lower yields. The decrease in the yields of cycloadducts was also observed with zinc(II) chloride (Table 1, entries 2, 7 and 12) as catalyst. An increase in yields was noticed in the reactions of 6-morpholine substituted 5-dienyl pyrimidinones **1c**, as dienophiles (Table 1, entries 1–15).

In contrast to the high yields of cycloadducts obtained in the reactions of **1a**–**c** with **2a**–**c**, the reactions of **1a**–**c** with imine **2d** in the presence of the Lewis acid catalysts mentioned above resulted in poor yields of the corresponding aza DA cycloadducts (Scheme 1, Table 2, entries 1–5).

These reactions were also conducted in the presence of a mixed Lewis acid (15 mol% of magnesium(II) bromide and a catalytic amount of aluminium(III) chloride) in dry dichloromethane. This was done with a view to increase the efficiency as well as yields by possible formation of an active $MgBr^+$ cation which is sufficiently acidic to activate the imines (Eq. 1). As expected, excellent yields were obtained in these reactions (Table 2, entry 6). Surprisingly, the reaction did not proceed in the presence of a stoichiometric amount of aluminium(III) chloride, possibly due to imine hydrolysis because of the strong acidity.

$$AlCl_3 + MgBr_2 \rightarrow [MgBr]^+[AlCl_3Br]^- \qquad (1)$$

Table 1. Lewis acid catalysed reactions of **1a–c** with various imines

Entry	Pyrimidinone	Imine	Lewis acid	Yield (%)
1	**1a/b/c**	**2a**	$MgBr_2$	83/81/88
2	**1a/b/c**	**2a**	$ZnCl_2$	43/44/49
3	**1a/b/c**	**2a**	$InCl_3$	69/65/72
4	**1a/b/c**	**2a**	$Y(OTf)_3$	72/73/79
5	**1a/b/c**	**2a**	$Sc(OTf)_3$	75/74/81
6	**1a/b/c**	**2b**	$MgBr_2$	82/88/90
7	**1a/b/c**	**2b**	$ZnCl_2$	43/52/60
8	**1a/b/c**	**2b**	$InCl_3$	63/62/62
9	**1a/b/c**	**2b**	$Y(OTf)_3$	68/72/78
10	**1a/b/c**	**2b**	$Sc(OTf)_3$	68/70/74
11	**1a/b/c**	**2c**	$MgBr_2$	75/77/86
12	**1a/b/c**	**2c**	$ZnCl_2$	42/43/48
13	**1a/b/c**	**2c**	$InCl_3$	71/70/78
14	**1a/b/c**	**2c**	$Y(OTf)_3$	65/69/78
15	**1a/b/c**	**2c**	$Sc(OTf)_3$	67/71/84

All the reactions resulted in the formation of single cycloadducts and were conducted at room temperature. For indium(III) chloride, scandium triflate and yttrium triflate, acetonitrile was used as the solvent. For magnesium(II) chloride and zinc(II) chloride, dry dichloromethane was used as the solvent.

Table 2. Lewis acid catalyzed reactions of **1a–c** with *N*-benzylidene anilines

Entry	Pyrimidinone	Imine	Lewis acid	Yield (%)
1	**1a/b/c**	**2d**	$MgBr_2$	8/5/10
2	**1a/b/c**	**2d**	$ZnCl_2$	9/10/12
3	**1a/b/c**	**2d**	$InCl_3$	11/15/14
4	**1a/b/c**	**2d**	$Y(OTf)_3$	16/19/19
5	**1a/b/c**	**2d**	$Sc(OTf)_3$	14/16/20
6	**1a/b/c**	**2d**	$MgBr_2$/cat. $AlCl_3$	74/75/86

All the reactions resulted in the formation of single cycloadducts and were conducted at room temperature, For indium(III) chloride, scandium triflate and yttrium triflate, dry acetonitrile was used as the solvent while for magnesium(II) chloride, zinc(II) chloride and $MgBr_2$/cat. $AlCl_3$, dry dichloromethane was used as the solvent.

The isolated products were characterised on the basis of analytical data and spectral evidence[14] with the salient spectral features discussed here. For example, **4g**, showed a $[M+1]^+$ peak at m/z 593. Its IR spectrum showed a strong absorption at 1665 cm^{-1} due to the carbonyl group of the pyrimidinone ring. The high resolution ^1H NMR (600 MHz) spectrum showed a singlet at

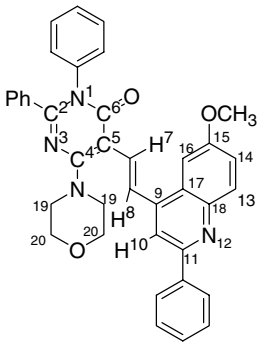


Figure 1. Structure of **4g**.

3.91 due to the $-OCH_3$ of the quinoline ring, two doublets at δ 7.18 ($J = 16.3$ Hz) and δ 8.49 ($J = 16.3$ Hz) due to H^8 and H^7, a characteristic singlet at δ 7.87 due to H^{10} of the quinoline ring, two doublets at δ 7.58 ($J = 9.0$ Hz) and δ 7.41 ($J = 2.7$ Hz) due to the H^{13} and H^{16} protons and a doublet of doublets at δ 7.35 ($J = 2.7$, 9.0 Hz) assigned to H^{14} of the quinoline ring (Fig. 1).

In conclusion, we have reported a Lewis acid/mixed Lewis acid mediated imino DA reaction of unactivated *N*-arylimines with unactivated acyclic 1,3-butadienes resulting in a variety of novel quinoline/pyrimidinone derivatives in good yields. A possible reason for the unusual 2π-behaviour of 1-substituted butadienes in such aza Diels–Alder cycloaddition reactions may be due to the expected steric interaction between the pyrimidinone ring and the aryl group present on the nitrogen of the *N*-aryl imines in the normal DA adducts when the diene group attached to the pyrimidinone ring participates as a 4π component. Alternatively, it may be due to activation of the terminal double bond by the slight polarisation of the dienyl group involving the non-bonding electron present on N^3 of the pyrimidinone ring. It is also possible that ring closure leading to the formation of 5-quinoline substituted pyrimidinone derivatives may be the result of a sequence of electrophilic additions and substitution reactions as shown below (Fig. 2).

In order to distinguish between these mechanistic possibilities, further work is in progress in our laboratory.

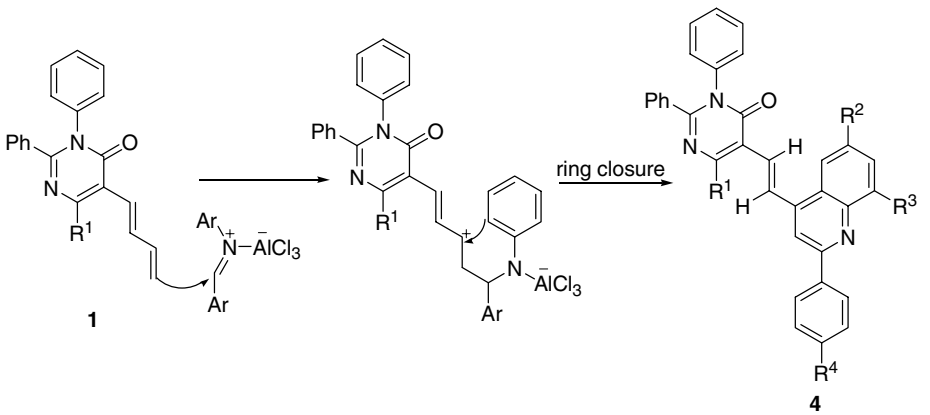


Figure 2.

Acknowledgement

We are thankful to Professor Takao Saito, Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan for providing 600 MHz NMR spectra.

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14. *5-[2-(6-Methoxy-2-phenyl-quinolin-4-yl)-vinyl]-6-morpholin-4-yl-2,3-diphenyl-3H-pyrimidin-4-one* (**4g**): Mp 183–184 °C; ^{1}H NMR (600 MHz, $CDCl_3$, Me_4Si): δ 3.75 (m, 4H, $-H_{morpholine}$), 3.84 (m, 4H, $H_{morpholine}$), 3.91 (s, 3H, $-OCH_3$), 7.18 (d, 1H, $J = 16.3$ Hz, H^8), 7.25 (m, 15H, $H_{aromatic}$); 7.35 (dd, 1H, $J = 2.7$, 9.0 Hz, H^{14}), 7.41 (d, 1H, $J = 2.7$ Hz, H^{16}), 7.58 (d, 1H, $J = 9.0$ Hz, H^{13}), 7.87 (s, 1H, H^{10}), 8.49 (d, 1H, $J = 16.3$ Hz, H^7); ^{13}C NMR (150 MHz, $CDCl_3$, Me_4Si): δ 49.8 (–C morpholine), 55.7 ($-OCH_3$), 67.1 (–C morpholine), 99.2, 101.9, 114.1, 122.1, 124.6, 126.4, 127.3, 127.9, 128.4, 128.5, 128.9, 129.0, 129.0, 129.2, 129.9, 131.4, 134.6, 134.8, 137.5, 138.6, 144.5, 144.7, 153.5, 155.6, 157.7, 161.7, 162.7; IR(KBr) ν_{max}: 1665 cm^{-1}; MS: m/z $[M+1]^+$: 593; Anal. Calcd for $C_{38}H_{32}N_4O_3$: C, 77.01; H, 5.44; N, 9.45. Found: C, 77.19; H, 5.57; N, 9.32.