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An unprecedented methylene oxidation accompanying the aza Diels–Alder reactions of acyclic unactivated alkenes: synthesis of novel quinolin-3-one substituted pyrimidinone derivatives

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Abstract—The regioselective aza Diels–Alder reactions of isopropenyl pyrimidinone with *N*-arylimines in the presence of Y/Sc triflates as catalyst are described. An unprecedented oxidation of methylene to carbonyl occurred resulting in exclusive formation of 6-oxo-1,6-dihydropyrimidin-5-yl-4*H*-quinolin-3-one derivatives.

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] Reviews featuring the synthetic utility of imino Diels–Alder reactions of imines with dienes or alkenes in the presence of Lewis acids have appeared in recent years.[3,4] The key to realising this potential lies in the fact that the imine system needs to be activated or has to be used in conjunction with dienes activated towards the cycloaddition reaction. There are numerous reports concerning Lewis acid catalysed aza Diels–Alder reactions restricted to the use of unhindered, activated alkenes thus leading to the synthesis of tetrahydro/dihydroquinoline ring derivatives.[5] However, there is hardly any report on Lewis acid catalysed hetero Diels–Alder reactions of unactivated and hindered alkenes. In view of the unique properties of Lewis acids in increasing the selectivity in various organic reactions and as a part of our continued interest in the synthesis of biologically important heterocycles,[6] it was thought worthwhile to compare the dienic properties of C-5 isopropenyl substituted pyrimidinone derivatives with functionalised imines by examining their reactions in the presence of various Lewis acids. We report herein, an unexpected methylene oxidation accompanying the regioselective aza Diels–Alder reactions of *N*-arylimines (2-azadienes) with unactivated alkenes, that is C-5 substituted isopropenyl pyrimidinone derivatives, in the presence of $Y(OTf)_3$ and $Sc(OTf)_3$.

Treatment of *N*-arylimine **2** with C-5 substituted isopropenyl pyrimidinone **1** in the presence of 10 mol % $Y(OTf)_3/Sc(OTf)_3$ in acetonitrile at room temperature, followed by purification of the crude reaction mixture by silica gel chromatography resulted in 6-oxo-1,6-dihydro-pyrimidin-5-yl-4*H*-quinolin-3-one derivatives **5** in good yields (73–88%) (Scheme 1). The isolated products were characterised on the basis of analytical data and spectral evidence.[7] The salient features of the ^1H NMR spectrum of **5a**, for example, showed the absence of methylene protons, the presence of a three proton singlet at δ 1.73 due to the quinolin-3-one ring methyl protons and a characteristic singlet at δ 8.34 for the olefinic proton of the pyrimidinone ring. The ^{13}C NMR spectrum showed characteristic absorbances at δ 160.5 and 193.7 ppm for the pyrimidinone and quinolin-3-one ring carbonyls, respectively. The IR spectrum showed carbonyl absorptions at 1666 and 1687 cm^{-1}, whilst the mass spectrum exhibited a $(M^{+}+1)$ peak at $m/z = 546$. The structure was unambiguously established with the help of X-ray crystallographic studies (Fig. 1).[8] The observed methylene oxidation accompanying the hetero Diels–Alder reaction was generalised by examining the reactions of various *N*-arylimines with C-5 isopropenyl substituted pyrimidinones, all of which resulted in the formation of 6-oxo-1,6-dihydro-pyrimidin-5-yl-4*H*-quinolin-3-one derivatives (Table 1).

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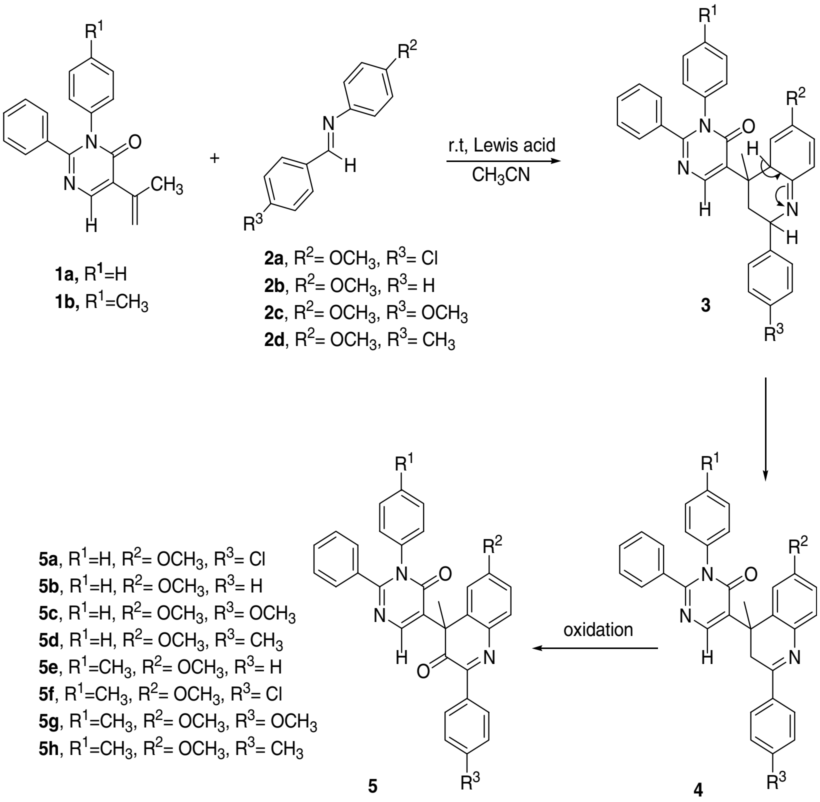

Scheme 1.

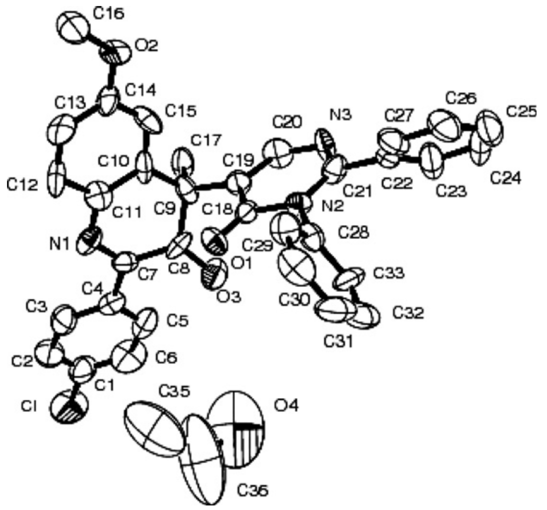

Figure 1. ORTEP diagram of **5a**.

Table 1. Lewis acid catalysed reactions of **1a**–**b** with imines **2a**–**d**[a]

Entry	Product	Lewis acid	R^1	R^2	R^3	Yield[b] (%)
1	**5a**	$Y(OTf)_3$	H	OCH_3	Cl	82
2	**5b**	$Y(OTf)_3$	H	OCH_3	H	88
3	**5c**	$Y(OTf)_3$	H	OCH_3	OCH_3	79
4	**5d**	$Y(OTf)_3$	H	OCH_3	CH_3	75
5	**5e**	$Y(OTf)_3$	CH_3	OCH_3	H	85
6	**5f**	$Y(OTf)_3$	CH_3	OCH_3	Cl	77
7	**5g**	$Y(OTf)_3$	CH_3	OCH_3	OCH_3	79
8	**5h**	$Y(OTf)_3$	CH_3	OCH_3	CH_3	80
9	**5a**	$Sc(OTf)_3$	H	OCH_3	Cl	73
10	**5b**	$Sc(OTf)_3$	H	OCH_3	H	79
11	**5c**	$Sc(OTf)_3$	H	OCH_3	OCH_3	76
12	**5d**	$Sc(OTf)_3$	H	OCH_3	CH_3	75
13	**5e**	$Sc(OTf)_3$	CH_3	OCH_3	H	84
14	**5f**	$Sc(OTf)_3$	CH_3	OCH_3	Cl	81
15	**5g**	$Sc(OTf)_3$	CH_3	OCH_3	OCH_3	78
16	**5h**	$Sc(OTf)_3$	CH_3	OCH_3	CH_3	76

[a] All the reactions were conducted separately using CH_3CN as solvent.
[b] Yields were measured prior to crystallisation.

It is hypothesised that the formation of the products involves regioselective imino Diels–Alder reactions in which the *N*-arylimine participates as a 4π component leading to the initial formation of cycloadduct **3**, which on aromatisation followed by oxidation[9] gives the product **5**. The unprecedented oxidation of methylene to carbonyl accompanying these reactions may be envisioned as taking place through an obscure mechanism similar to that accompanying the $Yb(OYf)_3$ promoted Cannizzaro reaction of arylmethyl ketones[10] and the $Ce(OTf)_4$ catalysed benzylic oxidation of aromatics,[11] which takes place via a charge transfer complex followed by the formation of a radical cation by electron transfer. Analogously, it is presumed that a radical cation is formed on the CH_2 attached to the C=N of the quinoline ring, which is quenched with water/methanol (during work-up) to give an alcohol, further oxidation of which yields the carbonyl compound **5**.

In conclusion, the reactions of isopropenyl pyrimidinones **1** with *N*-arylimines **2** in the presence of $Y(OTf)_3/Sc(OTf)_3$ result in a tandem aza Diels–Alder reaction of sterically hindered, unactivated alkenes and methylene oxidation leading to the exclusive formation of 6-oxo-1,6-dihydro-pyrimidin-5-yl-4*H*-quinolin-3-one derivatives **5**. Moreover, the reaction described herein represents, to the best of our knowledge, the first example of the oxidation of a methylene attached to C═N during aza Diels–Alder reactions of imines.

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7. *2-(4-Chlorophenyl)-6-methoxy-4-(6-oxo-1,2-diphenyl-1,6-dihydropyrimidin-5-yl)-4H-quinolin-3-one* **5a**: Mp 161–162 °C. Yield: 82%; IR (KBr) ν_{max}: 1666 cm^{-1}, 1687 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Me_4Si): δ 1.73 (s, 3H, $-CH_3$), 3.84 (s, 3H, $-OCH_3$), 6.65–7.99 (m, 17H, arom), 8.34 (olefinic proton); ^{13}C NMR (150 MHz, $CDCl_3$, Me_4Si): δ 24.8 ($-CH_3$), 51.1 (C-7, quinolin-3-one ring), 55.5 ($-OCH_3$), 111.4, 112.7, 123.6, 127.9, 128.0, 128.4, 128.6, 128.65, 128.8, 129.0, 129.2, 129.8, 129.9, 132.7, 134.3, 134.9, 135.3, 136.6, 138.8, 149.4, 154.1, 159.3, 160.3, 160.5 (C═O, pyrimidinone ring), 193.7 (C═O, quinolin-3-one ring); MS: *m*/*z* $[M+1]^+$: 546. Anal. Calcd for $C_{33}H_{24}ClN_3O_3$: C, 72.59; H, 4.43; N, 7.70; Found C, 72.71; H, 4.54; N, 7.79.
8. *Crystal data for* **5a**: CCDC reference: CCDC 626297, $C_{33}H_{24}ClN_3O_3$, $M = 545.15$, space group, monoclinic, $C2/c$, $a = 22.577(5)$ Å $\alpha = 90.000(5)°$, $b = 13.992(5)$ Å $\beta = 96.270(5)°$, $c = 18.851(5)$ Å $\gamma = 90.000(5)°$, $V = 5919(3)$ A^3, $Z = 4$, $D_{calcd} = 1.322$ mg/m^{-3}, $T = 293(2)$ K, radiation = 0.71073 Å, final R indices $[I > 2\sigma(I)]$, $R_1 = 0.0705$, $wR_2 = 0.1846$, R indices (all data), $R_1 = 0.2769$, $wR_2 = 0.2723$, for all data total reflections collected/unique 3978/3829 [R(int) = 0.1088], GOF = 0.747. Diffraction data were measured on a Siemens 4 Circle Single Crystal X-ray diffractometer.
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