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N-Allyl-1,3-oxazines via a facile keto-ene/cyclization tandem reaction ☆

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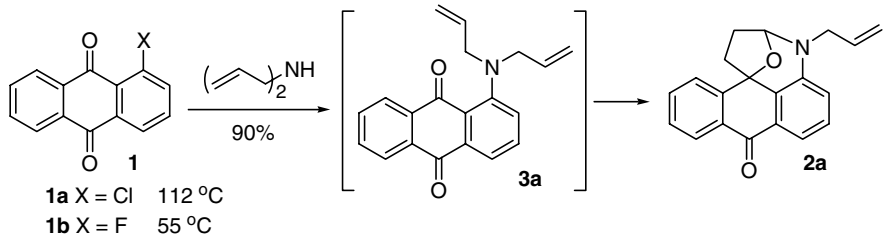
Abstract—The intramolecular keto-ene/cyclization tandem reaction of γ-*N*-allylamino ketones is an effective means of producing 1,3-oxazines. The reaction usually requires high temperatures and/or pressures. We discovered that *N*,*N*-diallyl amines undergo the reaction at lower temperatures than their monoallyl analogs. An extreme example, 1-*N*,*N*-diallylamino-9,10-anthraquinone, undergoes the keto-ene reaction near ambient temperature. In the case of 1-*N*,*N*′-dialkylaminoanthraquinones, electron deficient ene components can even be used, allowing the preparation of a broad spectrum of oxazines. Furthermore, the *N*-allyl-1,3-oxazine can be easily deallylated to produce a 1,3-oxazine that contains a secondary amine.

1,3-Oxazines and azepines have generated interest as anti-psychotic agents and as possible effectors for serotonin and dopamine receptors.[1–3] In addition, benzoxazines have been evaluated as anti-malarial agents.[4] Recent reports describing the preparation of these ring systems use *N*-allylamino ketones and aldehydes in intramolecular ene and keto-ene reactions.[5–7] To date, the keto-ene reactions reported occur only when high temperatures (>150 °C) or unusually electrophilic carbonyls are used in conjunction with nucleophilic alkenes.

In the course of studying 1-(*N*,*N*-diallyldialkylamino)-9,10-anthraquinones, we discovered that the incorporation of a second allyl group on the amine nitrogen lowers the barrier to the keto-ene reactions, often dramatically. In some cases, we have found examples of a keto-ene/cyclization tandem reaction that occur at 25 °C. In all cases examined, the diallylamine underwent the reaction at lower temperature than the monoallylamines.

When 1-chloro-9,10-anthraquinone **1a** was treated with neat, refluxing *N*,*N*-diallylamine, 1,3-oxazine **2a** was isolated in 90% yield instead of the expected 1-(*N*,*N*-diallylamino)-9,10-anthraquinone **3a** (Scheme 1).[8] Attempts to isolate **3a** failed. Addition of *N*,*N*-diallylamine to 1-fluoro-9,10-anthraquinone, **1b**, did not proceed below 55 °C. Even at this temperature, 1,3-oxazine **2a**



Scheme 1.

Keywords: Keto-ene; Tandem reaction; 1,3-Oxazine; Anthraquinone.
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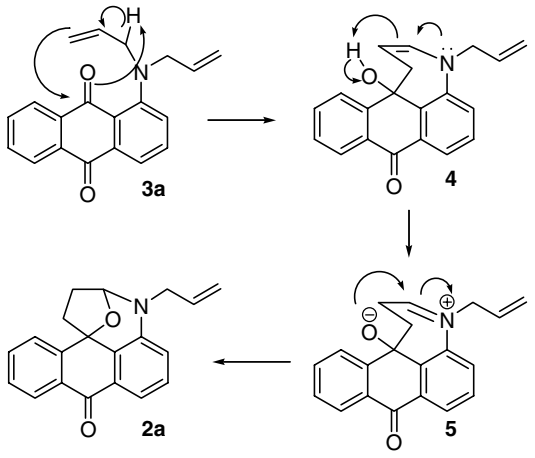


Scheme 2.

was the only isolable product. The structure of 1,3-oxazine **2a** was determined by 2-D NMR experiments.

Scheme 2 illustrates the proposed type II mechanism for the keto-ene reaction[9] and subsequent cyclization. After substitution of the amine, proton transfer from the allylic methylene group to the quinone oxygen, followed by rapid cyclization, produced azepine **4**. A second proton transfer generated an iminium salt **5**, which rapidly cyclized to the 1,3-oxazine **2a**. The presence of two allyl groups ensures that one alkene is proximal to the carbonyl and allows the reaction to proceed at reduced temperature.

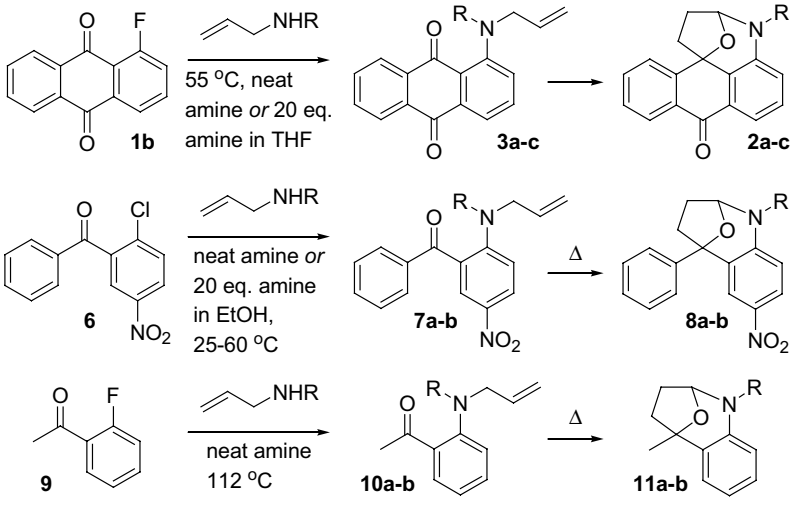
To investigate the scope of this reaction, a series of 1-(*N*-allyl-*N*-alkylamino)-arylketones was synthesized (Scheme 3). All were prepared in moderate to excellent yield (50–90%). As with **3a**, 1-(*N*-allyl-*N*-cyclopentylamino)-9,10-anthraquinone **3c** was not isolable. 1-(*N*-Methyl-*N*-allylamino)-9,10-anthraquinone **3b** was the only 1-(*N*,*N*-α,β-unsaturated-dialkylamino)-9,10-anthraquinone isolated. This compound slowly underwent the keto-ene/cyclization tandem reaction on standing at room temperature. At 25 °C, this conversion was complete in 10 days. Upon heating **3b** in refluxing THF for 7 h **2b** was obtained cleanly in 95% yield. Incorporation of a bulky alkyl group on the amine nitrogen caused the keto-ene/cyclization tandem reaction to occur more rapidly than the preceding aromatic substitution reaction, rendering the amino-9,10-anthraquinone unisolable. Hence, the reaction of *N*-cyclopentyl-*N*-allylamine and **1b** in refluxing THF provided **2c** in 63% yield; the S_NAr reaction was very sluggish at temperatures below 60 °C. The major product **2c** suggested that the bulky cyclopentyl group forces the allyl group toward the carbonyl, increasing the rate of keto-ene cyclization.

Benzophenones **7a–b** and acetophenones **10a–b** underwent the keto-ene cyclization at temperatures more in line with literature precedent.[4] However, 2-(*N*,*N*-diallylamino)-5-nitrobenzophenone **7a** and 2-(*N*,*N*-diallylamino)-acetophenone **10a** showed increased reactivity when compared to the 2-(*N*-methyl-*N*-allylamino)-5-nitrobenzoquinone **7b** and 2-(*N*-methyl-*N*-allylamino)-acetophenone **10b** (Table 1). For example, **7a** was converted to **8a** in 74% yield upon heating to 140 °C for

Table 1. Results of keto-ene/cyclization of amino ketones **7** and **10** to give 1,3-oxazines **8** and **11**, respectively

Entry	Substrate	Time (h)	% Yield	*T* (°C)
1	**7a**	120	0	110
2	**7a**	120	74	140
3	**7b**	120	0	140
4	**7b**	72	65	165
5	**10a**	120	29	140
6	**10b**	120	Trace	140
7	**10a**	96	40	165
8	**10b**	120	28	165
9	**10a**	120	68	230[a]
10	**10b**	120	72	230[a]

[a] Sealed tube; mesitylene solvent.



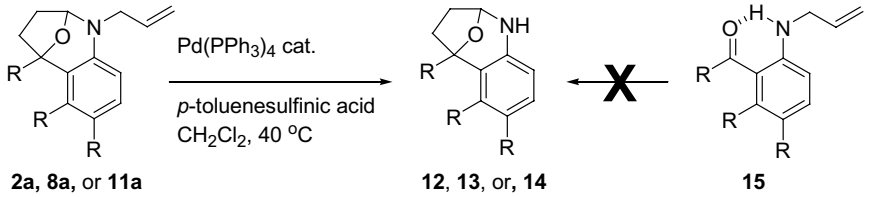
Scheme 3.

120 h while **7b** did not react at all under identical conditions (entries 2 and 3).[10] Similarly, **10a** rearranged to **11a** in 29% yield after 120 h at 140 °C (entry 5).[11] The same conditions produced only a trace of **11b** from **10b** (entry 6). The same trend can be seen in the 9,10-anthraquinone series; **3a** was not isolable while **3b** could be isolated at ambient temperature. In each case, the incorporation of a second allyl group on the amine nitrogen lowered the temperature required for the keto-ene/cyclization tandem reaction.

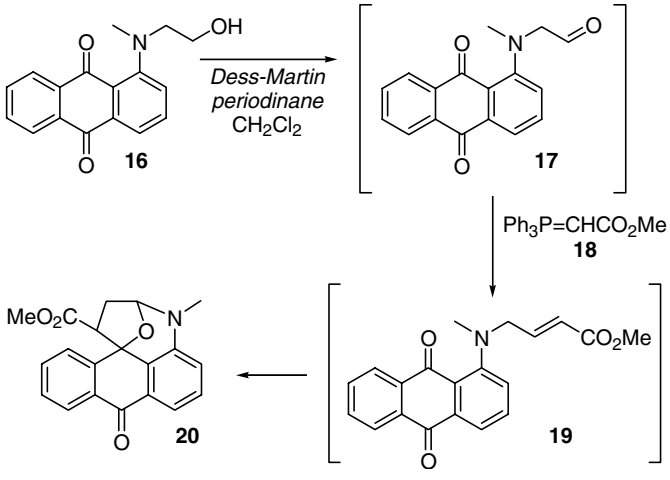
Importantly, the allyl group was easily removed from the *N*-allyl-1,3-oxazine. Using the conditions of Nagakura and co-workers,[12] catalytic Pd(0) and *p*-toluenesulfinic acid in refluxing methylene chloride cleaved the allyl group from **2a** to afford the secondary amine **12** in 58% yield (Scheme 4). Similar results were obtained for *N*-allyl-1,3-oxazines **8a** and **11a**; **13** and **14** were obtained in 64% and 55% yields, respectively.[13] Thus, the incorporation of a diallylamine in the keto-ene reaction not only allowed the use of milder conditions but also yielded *N*-allyl-1,3-oxazines that could be easily dealkylated to give a 1,3-oxazine containing a secondary amine. The keto-ene/cyclization tandem reaction (e.g., **15** → **14**) that would give such *N*-protio-1,3-oxazines does not occur, due to a strong hydrogen bond between the N–H and carbonyl oxygen and preference for the allyl group to be oriented away from the carbonyl.

Given the ease with which anthraquinones **3a**–**c** underwent the keto-ene cyclization, we speculated that even an electron deficient alkene might be induced to undergo the keto-ene reaction. In order to test this hypothesis, **16** was prepared by addition of *N*-methyl-2-aminoethanol to **1a** in refluxing toluene. Oxidation of **16** proved difficult, as aldehyde **17** dealkylated easily to afford 1-methylamino-9,10-anthraquinone. However, **16** could be converted to **20** in one pot; oxidization of **16** to **17** with Dess–Martin periodinane in the presence of stabilized ylide **18** gave **19**. The latter proved unisolable due to the predicted keto-ene/cyclization tandem reaction. When the reaction was carried out at 40 °C, oxazine **20** was obtained in 74% yield from **16**.[14] Thus, the keto-ene reaction of **19** was very efficient despite the electron deficient nature of the alkene component. This reaction demonstrates that the keto-ene cyclization of analogs of **3** should tolerate a wide range of functionality on the alkene unit (Scheme 5).

In summary, we have found that diallylamines, such as **3a**, undergo a keto-ene/cyclization tandem reaction at lower temperature than their monoallyl analogs. In some cases, this allows the formation of 1,3-oxazines at or near ambient temperatures. In addition, the resulting *N*-allyl-1,3-oxazine can be easily converted to a 1,3-oxazine with a secondary amine, which cannot be obtained directly via a keto-ene/cyclization involving a secondary amine. In the case of 1-*N*,*N*′-dialkylamino-9,10-anthraquinones, even electron deficient alkenes can participate as the ene component of the keto-ene reaction, which is unprecedented and may allow a great deal of structural flexibility in the construction of oxazines.



Scheme 4. Pd(0) catalyzed deallylation of *N*-allyl oxazines.



Scheme 5. Cyclization of an electron deficient alkene.

Acknowledgements

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8. Data for **2a**: mp 78–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.12–2.36 (m, 2H), 2.42–2.54 (m, 2H), 3.83–4.08 (m, 2H), 5.19–5.24 (m, 1H), 5.30–5.37 (m, 1H), 5.50–5.52 (d, $J = 5.8$ Hz, 1H), 5.87–5.99 (m, 1H), 6.83–6.86 (dd, $J = 0.6$, 8.1 Hz, 1H), 7.26–7.32 (t, $J = 8.1$ Hz, 1H), 7.47–7.57 (m, 2H), 7.63–7.69 (m, 1H), 7.85–7.88 (m, 1H), 8.21–8.24 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.2, 142.9, 141.6, 133.8, 133.4, 131.2, 130.4, 128.8, 128.5, 128.1, 127.0, 124.4, 117.6, 116.9, 116.4, 91.1, 78.7, 53.9, 47.6, 35.9. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 78.95; H, 5.58; N, 4.55.
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10. Data for **8a**: mp 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.32–2.41 (m, 2H), 2.51–2.71 (m, 1H), 2.72–2.80 (m, 1H), 3.95–4.16 (m, 2H), 5.27–5.39 (m, 3H), 5.83–5.96 (m, 1H), 6.47–6.50 (d, $J = 9.0$ Hz, 1H), 7.31–7.32 (d, $J = 2.6$ Hz, 1H), 7.36–7.54 (m, 5H), 7.94–7.98 (dd, $J = 2.6$, 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.0, 140.2, 137.1, 131.7, 130.0, 128.6, 128.4, 127.0, 125.3, 121.4, 117.5, 109.8, 89.7, 87.5, 51.1, 40.6, 36.1. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.36; H, 5.64; N, 8.53.
11. Data for **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74 (s, 3H), 1.81–1.95 (m, 1H), 2.01–2.11 (m, 1H), 2.17–2.30 (m, 2H), 3.77–3.99 (m, 2H), 5.13–5.19 (m, 2H), 5.26–5.33 (m, 1H), 5.87–5.99 (m, 1H), 6.64–6.67 (d, $J = 8.1$ Hz, 1H), 6.69–6.74 (td, $J = 0.9$, 7.5 Hz, 1H), 7.03–7.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.3, 135.0, 131.7, 127.8, 122.9, 118.0, 116.4, 114.7, 90.1, 82.1, 54.8, 43.1, 34.2, 22.2. Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 8.11; N, 6.51. Found: C, 77.87; H, 7.84; N, 6.40.
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13. Data for **13**: mp 200 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.27–2.48 (m, 2H), 2.52–2.62 (m, 1H), 2.77–2.85 (m, 1H), 5.38 (br s, 1H), 5.54–5.58 (m, 1H), 6.52–6.55 (d, $J = 8.7$ Hz, 1H), 7.36–7.54 (m, 6H), 7.92–7.95 (dd, $J = 2.6$, 8.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.1, 140.1, 138.7, 130.5, 128.7, 128.4, 127.0, 124.8, 122.0, 113.8, 86.6, 83.8, 41.1, 37.0. Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.96; H, 4.95; N, 9.79.
14. Data for **20**: mp 93–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.40 (dd, $J = 9.0$, 12.9 Hz, 1H), 2.93 (m, 1H), 3.02 (s, 3H), 3.03 (s, 3H), 3.44 (dd, $J = 4.8$, 9.0 Hz, 1H), 5.54 (d, $J = 6.0$ Hz, 1H), 6.85 (d, $J = 0.9$, 8.1 Hz, 1H), 7.55 (m, 5H), 8.23 (dd, $J = 1.2$, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.1, 171.5, 158.6, 141.8, 139.0, 132.6, 131.9, 129.8, 129.2, 128.7, 127.3, 124.7, 117.6, 116.6, 92.2, 81.2, 60.9, 51.7, 37.5, 37.1. HRMS calcd for ($C_{20}H_{17}NO_4 + Na^+$): 358.104977. Found: 358.10548.