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Cite this: DOI: 10.1039/c0xx00000x

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## Communication

## Unusual tandem sequence of oxa Diels-Alder reaction, retro-Diels-Alder reaction and oxa 6π-electrocyclic ring-opening in the reaction of 6-amino-4-(4-methoxyphenyl)-2H-pyran-2-ones with benzaldehydes†

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DOI: 10.1039/b000000x

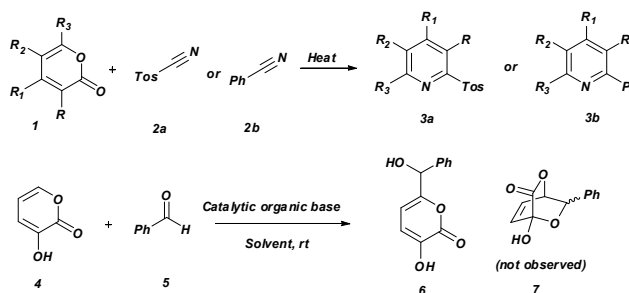
The oxa Diels-Alder reaction of 6-amino-4-(4-methoxyphenyl)-2H-pyran-2-ones with benzaldehydes took an unusual path; and through a tandem sequence of oxa Diels-Alder reaction, retro Diels-Alder reaction, and 6π-electrocyclic ring opening of the pyran yielded 3-(4-methoxyphenyl)-5-phenyl-1-(piperidin-1-yl/pyrroliden-1-yl)penta-2,4-dien-1-ones. The reaction took place in boiling toluene with a series of substituted benzaldehydes. An electron donating group on benzaldehyde retarded the reaction, while an electron withdrawing group favoured it; thus indicating the normal electron demand pathway.

2-Pyrones are function as dienes in the Diels-Alder reaction. The first Diels-Alder reaction of 2-pyrone was reported way back in 1931 by Otto Diels and Kurt Alder; only three years after the discovery of Diels-Alder reaction.<sup>1</sup> Subsequently, the reaction has been applied in the synthesis of various natural and synthetic products.<sup>2,3</sup> The application in synthesis and the utility of 2-pyrones has been described in reviews.<sup>4,5</sup> The reaction is interesting, as the intermediate bicyclic adduct undergoes rapid expulsion of carbon dioxide, through retro-Diels-Alder reaction, to form the carbocyclic product. There are a few reports in which the unstable bicyclic adduct has been isolated.<sup>6–8</sup> An electron donating group on the 2-pyrones ring favours the normal electron demand Diels-Alder reaction. The Diels-Alder reaction of 3-hydroxy-2-pyrones is accelerated in the presence of a base due to the formation of better electron donating oxide anion.<sup>9,10</sup> 3,5-dibromo-2-pyrone reacts with electron deficient as well as electron rich dienophiles and give normal and inverse electron demand Diels-Alder reactions, thus showing an ambident diene characteristic.<sup>8</sup> An electron donating group, like methyl or methoxyl group, at the 6-position of the 2-pyrones ring is highly favorable and the corresponding Diels-Alder reaction has been used to construct diverse skeletons.<sup>11,12</sup>

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterisation data of compounds, copies of NMR, HRMS spectra. See DOI: 10.1039/b000000x/

The Diels-Alder reactions of 2-pyrones reported so far are mostly carbocyclic. There are only a few reports of normal electron demand hetero Diels-Alder reaction of 2-pyrones (**1**) with nitrile group of toluene sulfonyl cyanide (**2a**) or benzonitrile (**2b**),<sup>14</sup> as hetero dienophile, to afford pyridine derivatives (**3a-b**). Interestingly, in an attempt to carry out the Diels-Alder reaction of 3-hydroxy-2-pyrone (**4**) with the carbonyl group of aromatic aldehydes (**5**), a vinylogous aldol reaction took place and 6-arylhydroxymethyl-3-hydroxy-2-pyrones (**6**) was formed, instead of the hetero Diels-Alder adduct (**7**) (Scheme 1).<sup>15</sup>

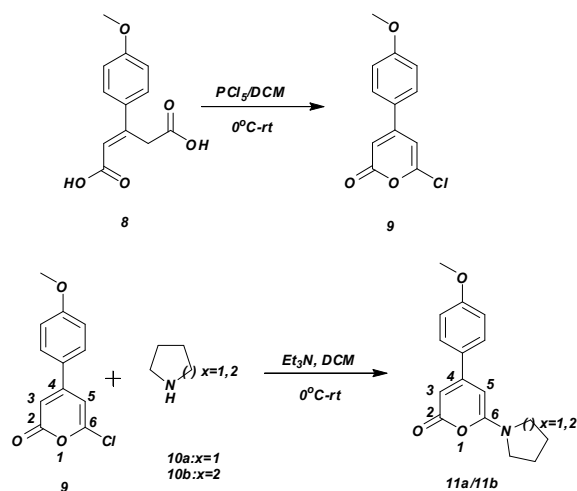


**Scheme 1** Previous attempts of hetero Diels-Alder reaction 2-pyrones

The normal electron demand Diels-Alder reaction of 2-pyrones is favored by an electron donating group in the 2-pyrones ring, particularly at 4- and 6-positions, and using an electron deficient dienophile. The carbonyl group of benzaldehydes is known to function as a dienophile in the hetero Diels-Alder reaction.<sup>16,17</sup> Hence, we thought that if a 2-pyrone is activated by an amino group at the 6-position, the pyrone would undergo a normal electron demand<sup>18</sup> oxa Diels-Alder reaction with the carbonyl group of an aryl aldehyde; the reaction would provide 2-aminopyrans. With this objective we attempted the Diels-Alder reaction of 6-amino-4-(4-methoxyphenyl)-2H-pyran-2-ones (**11**) with benzaldehydes (**12**). Unexpectedly, the Diels-Alder reaction gave 3,5-diaryl-1-aminopenta-2,4-dien-1-ones (**15** and **16**), through the expected Diels-Alder reaction followed by oxa 6π-electrocyclic ring opening of the initial adduct. This unusual reaction is described herein.

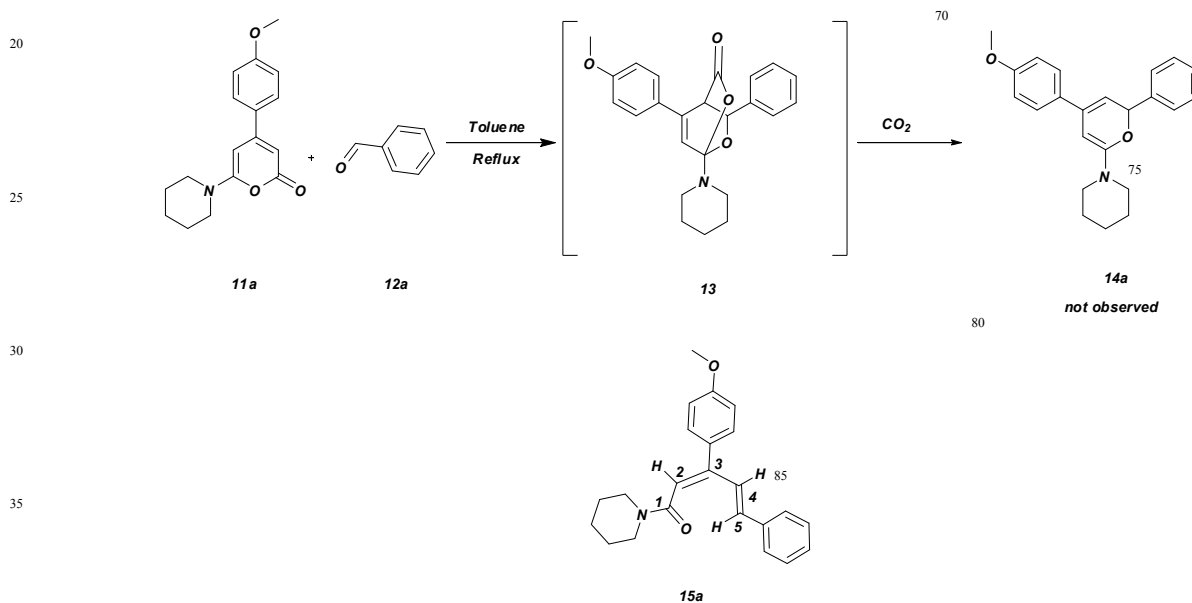
Acetone dicarboxylic acid was prepared by treating citric acid with conc. sulfuric acid and reacted with anisole *in situ* to obtain

3-(4-methoxyphenyl)pent-2-enedioic acid (**8**).<sup>19</sup> Conversion of 3-aryl-2-enedioic acid directly to 6-chloro-4-aryl-2-pyrone is known using  $\text{PCl}_5$  in chlorobenzene.<sup>20</sup> We used the similar condition for the conversion of **8** to **9**, but found that isolation of **9** from chlorobenzene solution was difficult and hence we replaced chlorobenzene with DCM. We recorded the m.p. of **9** as 110-112°C. Synthesis of **9** by some other procedure is known, interestingly the m.p. reported earlier is 216-217°C.<sup>21</sup> **9** on reaction with piperidine (**10a**) and pyrrolidine (**10b**) gave 6-amino-4-(4-methoxyphenyl)-2-pyrones **11a** and **11b**, respectively (Scheme 2).



Scheme 2 Synthesis of 6-amino-2-pyrones **11a** and **11b**

The Diels-Alder reaction of **11a** with benzaldehyde (**12a**) was attempted in refluxing toluene. The reaction was very slow; after 50 h the diene was almost consumed, and product **15a** was obtained. The expected product of the hetero-Diels-Alder reaction



Scheme 3 Hetero Diels-Alder reaction of **11a** with benzaldehyde

of **11a** with benzaldehyde (**12a**) under thermal conditions would be 2-aminopyran (**14a**); after the expulsion of  $\text{CO}_2$  from the

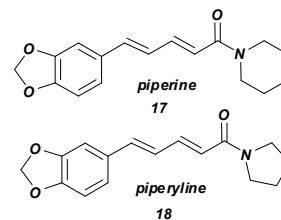
initial adduct **13** (Scheme 3). However, the product **15a** was found to be different than **14a**.

In the IR spectrum of **15a** there was a strong amide carbonyl peak at  $1619\text{ cm}^{-1}$ , the lower frequency was due to conjugated carbonyl group. In the  $^1\text{H NMR}$  spectrum of **15a**, the piperidine ring protons were intact along with the aromatic protons of both the phenyl rings; one of the diene and the other of the dienophile.

Interestingly, a pair of doublets, with *trans* coupling,  $J^2=16\text{ Hz}$ , due to olefinic protons were obtained at  $\delta\ 6.54$  and  $\delta\ 7.69$ . A third olefinic proton was observed at  $\delta\ 6.01$  as a singlet. The magnetically non-equivalent protons at  $\delta\ 3.52(2\text{H})$  and  $\delta\ 3.68(2\text{H})$  as two triplet hinted as piperidine amide moiety in the product. The structure was further confirmed by  $^1\text{H}-^1\text{H COSY}$  spectrum, the two *trans* coupling protons were seen at  $6.54$  and  $7.69\ \delta$ .

On the basis of the spectral analysis structure **14a** was ruled out and structure **15a** was assigned to the product. Thus, it appeared that the course of the reaction involved – formation of the initial Diels-Alder adduct **13**, which underwent decarboxylation to form 6-aminopyran **14a**; which in turn underwent  $6\pi$ -electrocyclic ring opening to form the product (2*E*,4*E*)-3-(4-methoxyphenyl)-5-phenyl-1-(piperidin-1-yl)penta-2,4-dien-1-one (**15a**).

This is in accord with the fact that 2*H*-pyran ring is unstable, and undergoes reversible ring opening to form open chain 1-oxodienes, even at ambient temperature.<sup>22-31</sup> Such 1-oxodienes find many synthetic applications.<sup>32-34</sup>

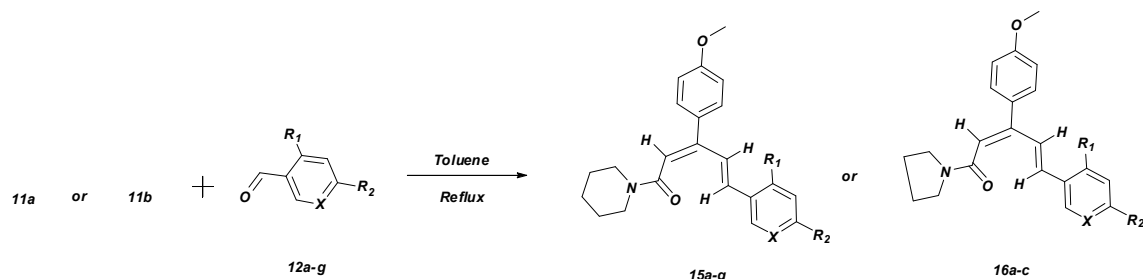


The dienamides **15** and **16** are interesting dienamic acid amides which are otherwise difficult to synthesize, as the respective dienamic acids are not available.

Cite this: DOI: 10.1039/c0xx00000x

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Table 1: Hetero-Diels-Alder reaction of 6-amino-2H-pyrones (**11**) with benzaldehydes (**12**)<sup>a</sup>

Entry	Pyrone	Benzaldehydes				Product	Time <sup>b</sup> (h)	Yield (%)	mp (°C)
		<b>12</b>	X	R <sup>1</sup>	R <sup>2</sup>				
1	<b>11a</b>	<b>12a</b>	C	H	H	<b>15a</b>	50	81	94-96
2	<b>11a</b>	<b>12b</b>	C	H	CN	<b>15b</b>	48	86	124-126
3	<b>11a</b>	<b>12c</b>	C	H	CF <sub>3</sub>	<b>15c</b>	32	84	112-114
4	<b>11a</b>	<b>12d</b>	N	H	H	<b>15d</b>	60	49	90-92
5	<b>11a</b>	<b>12e</b>	C	NO <sub>2</sub>	H	<b>15e</b>	38	56	100-102
6	<b>11a</b>	<b>12f</b>	C	CH <sub>3</sub>	H	<b>15f</b>	80	33	Gum
7	<b>11a</b>	<b>12g</b>	C	H	NO <sub>2</sub>	<b>15g</b>	40	73	128-130
8	<b>11b</b>	<b>12a</b>	C	H	H	<b>16a</b>	46	61	114-116
9	<b>11b</b>	<b>12b</b>	C	H	CN	<b>16b</b>	42	78	146-148
10	<b>11b</b>	<b>12c</b>	C	H	CF <sub>3</sub>	<b>16c</b>	42	79	122-124
11 <sup>c</sup>	<b>11a</b>		piperonal			-	80	-	-

a: Reaction conditions: **11a/b**: 0.5 mmol; **12**: 1 mmol; solvent: toluene (5 mL), reflux; b: complete consumption of **11a/b** c: no reaction

5 Further, such compounds are present in natural products. For example, piperine (**17**) and piperlyne (**18**) are pentadienoic acid amides, which are biologically active and are present in *Piper nigrum*.<sup>37-39</sup> Synthesis of these compounds often require multi step and cumbersome processes.<sup>35, 36</sup>

10 **11a** and **11b** were reacted with a series of substituted benzaldehydes (**12a-g**) in refluxing toluene to obtain a series of dienamides (**15a-g** and **16a-c**) (Table 1).

An electron donating group on benzaldehyde retarded the reaction; even methyl group gave poor yield (**10f**) and piperonal fails to furnish the product. On the other hand, electron withdrawing group like -CN, -CF<sub>3</sub>, -NO<sub>2</sub> gave excellent yield of the product.

### Conclusions

15 In conclusion, we have discovered, for the first time, an unusual reaction of 6-amino-4-(4-methoxyphenyl)-2H-pyran-2-ones with aromatic aldehydes involving a tandem sequence of normal electron demand Diels-Alder reaction, elimination of carbon dioxide from the adduct, and oxa-6π-electrocyclic ring opening of the pyran to form 3,5-diaryl-1-alkylamino-penta-2,4-diene-1-ones. The products pentadienoic acid amides are not common and are difficult to prepare; and hence, beside the theoretical interest, the reaction has a potential to furnish such unusual compounds.

### Acknowledgements

30 AIK is grateful to CSIR, Delhi (India), for a fellowship. The authors are thankful to Institute for Intensive Research in Basic Sciences (IIRBS), M. G. University, Kottayam, Kerala (India) and Guru Jambheshwar University of Science and Technology (GJUST), Harayana, (India) for providing NMR facility.

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## Graphical Abstract

