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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)-2*H*-pyran-2-ones with benzaldehydes†

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The oxa Diels-Alder reaction of 6-amino-4-(4-methoxyphenyl)-2*H*-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/pyrolliden-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.[1] Subsequently, the reaction has been applied in the synthesis of various natural and synthetic products.[2,3] The application in synthesis and the utility of 2-pyrones has been described in reviews.[4,5] 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.[6–8] 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.[9,10] 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.[8] 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.[11,12]

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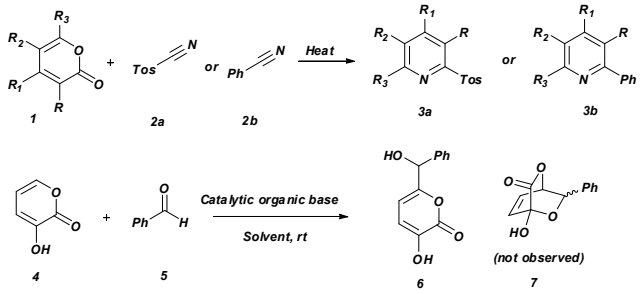
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterisation data of compounds, copies of NMR, HRMS spectra. See DOI: 10.1039/b000000x/

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[13] (**2a**) or benzonitrile (**2b**),[14] 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).[15]



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.[16,17] 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[18] 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)-2*H*-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

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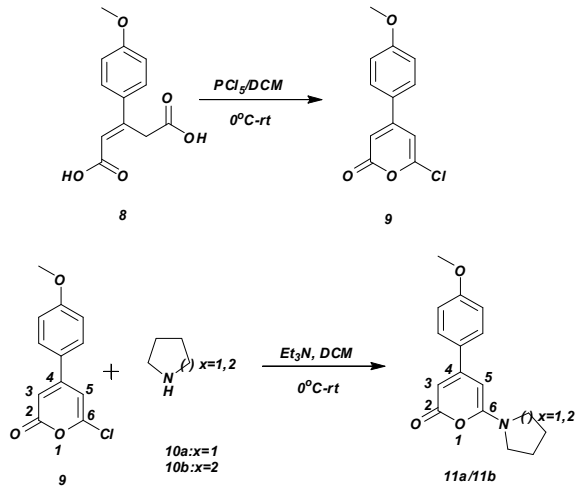
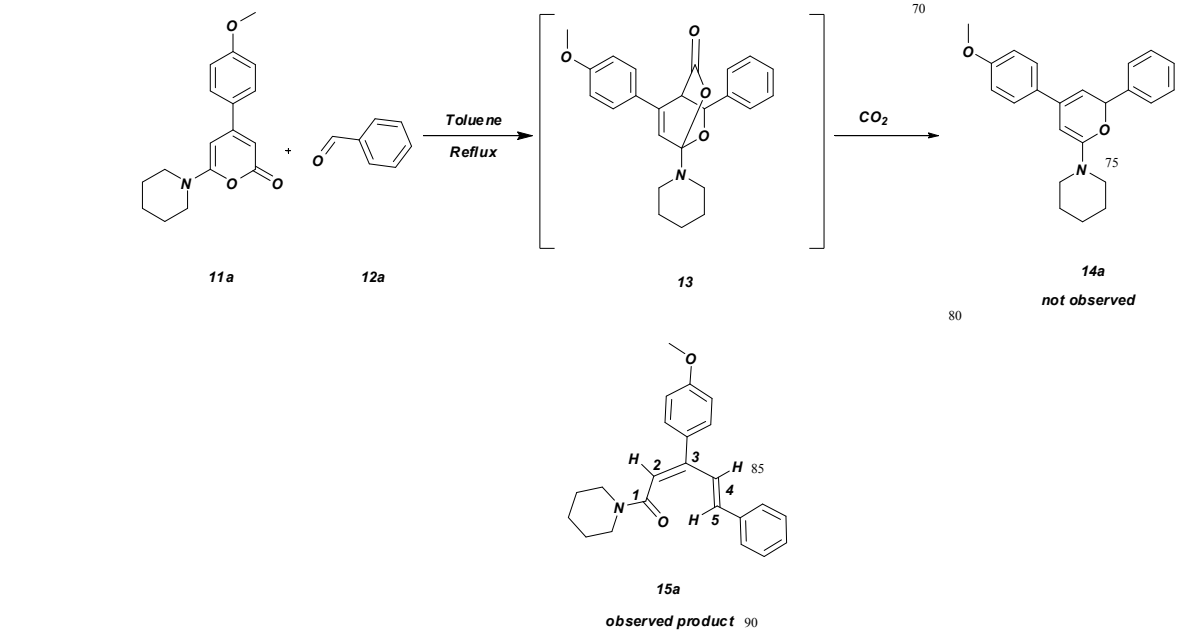
3-(4-methoxyphenyl)pent-2-enedioic acid (**8**).[19] Conversion of 3-arylpent-2-enedioc acid directly to 6-chloro-4-aryl-2-pyrone is known using PCl_5 in chlorobenzene.[20] We used the similar condition for the conversion of **8** to **9**, but found that isolation of **9** from chlorobenzene solution 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.[21] **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 of **11a** with benzaldehyde (**12a**) under thermal conditions would be 2-aminopyran (**14a**)**;** after the expulsion of CO_2 from the initial adduct **13 (Scheme 3)**. However, the product **15a** was found to be different than **14a**.

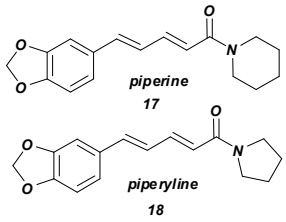


Scheme 3 Hetero Diels-Alder reaction of **11a** with benzaldehyde

In the IR spectrum of **15a** there was a strong amide carbonyl peak at 1619 cm^{-1}, the lower frequency was due to conjugated carbonyl group. In the ^1H 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 Hz, due to olefinic protons were obtained at δ 6.54 and δ 7.69. A third olefinic proton was observed at δ 6.01 as a singlet. The magnetically non-equivalent protons at δ 3.52(2H) and δ 3.68(2H) as two triplet hinted as piperidine amide moiety in the product. The structure was further confirmed by ^1H-^1H COSY spectrum, the two *trans* coupling protons were seen at 6.54 and 7.69 δ.

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 6π-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.[22–31] Such 1-oxodienes find many synthetic applications.[32–34]



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

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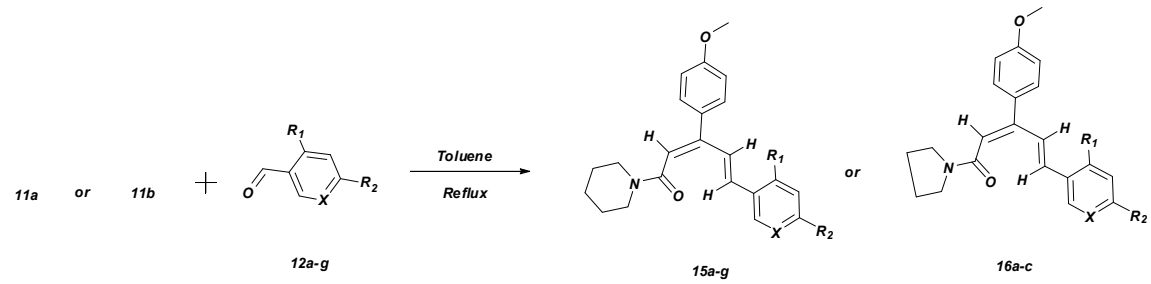
Table 1: Hetero-Diels-Alder reaction of 6-amino-2*H*-pyrones (**11**) with benzaldehydes (**12**)[a]



Entry	Pyrone	Benzaldehydes				Product	Time[b] (h)	Yield (%)	mp (°C)
		12	X	R^1	R^2				
1	**11a**	**12a**	C	H	H	**15a**	50	81	94-96
2	**11a**	**12b**	C	H	CN	**15b**	48	86	124-126
3	**11a**	**12c**	C	H	CF_3	**15c**	32	84	112-114
4	**11a**	**12d**	N	H	H	**15d**	60	49	90-92
5	**11a**	**12e**	C	NO_2	H	**15e**	38	56	100-102
6	**11a**	**12f**	C	CH_3	H	**15f**	80	33	Gum
7	**11a**	**12g**	C	H	NO_2	**15g**	40	73	128-130
8	**11b**	**12a**	C	H	H	**16a**	46	61	114-116
9	**11b**	**12b**	C	H	CN	**16b**	42	78	146-148
10	**11b**	**12c**	C	H	CF_3	**16c**	42	79	122-124
11[c]	**11a**	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

Further, such compounds are present in natural products. For example, piperine (**17**) and piperyline (**18**) are pentadienoic acid amides, which are biologically active and are present in *Piper nigrum*.[37–39] Synthesis of these compounds often require multi step and cumbersome processes. [35, 36]

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_3, -NO_2 gave excellent yield of the product.

Conclusions

In conclusion, we have discovered, for the first time, an unusual reaction of 6-amino-4-(4-methoxyphenyl)-2*H*-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.

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Graphical Abstract