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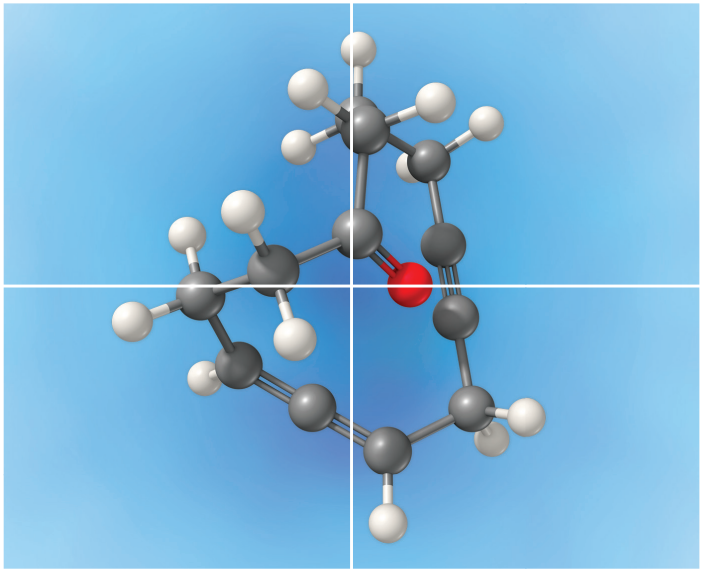

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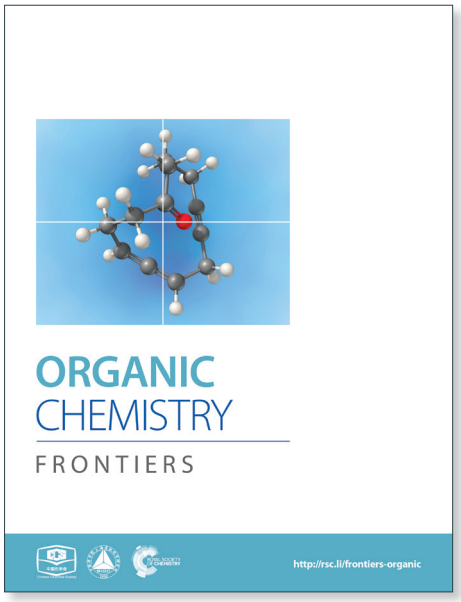

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ARTICLE TYPE

Revealing the dipolarophilic character of phthalic anhydrides: 1,3-dipolar cycloadditions with an azomethine ylide†‡

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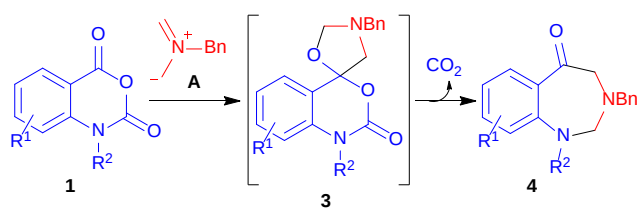
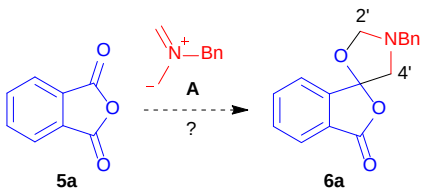
A series of phthalic anhydrides underwent a 1,3-dipolar cycloaddition reaction with *N*-benzylazomethine ylide, formed *in situ* from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine and a catalytic amount of trifluoroacetic acid, to produce unstable spiro(isobenzofuran-1,5'-oxazolidin)-3-ones. The spiro-fused oxazolidines were reduced with sodium borohydride to afford 1(3*H*)-isobenzofuranones, which were generally isolated in moderate to high overall yields.

The 1,3-dipolar cycloaddition reaction[1] of azomethine ylides with alkenes substituted with electron-withdrawing groups is an efficient and versatile method for the construction of pyrrolidine-containing molecules of biological[2] or materials science interest.[3] Less studied are the reactions with hetero multiple bonded systems; however carbonyl, thiocarbonyl, isothiocyanato, imino, isocyanato, nitrile, nitroso, and azo derivatives can also act as azomethine ylide dipolarophiles.[4,5] In the case of carbonyl dipolarophiles, aldehydes and ketones readily undergo cycloaddition reactions with azomethine ylides to give oxazolidines.[6] Generally carboxyl derivatives such as carboxylic acids and esters are unreactive in such reactions,[6d] although it has recently been demonstrated that certain activated carboxyl derivatives can act as azomethine ylide dipolarophiles.[7] The ester-like carbonyl group of isatoic anhydrides **1** undergoes a facile cycloaddition reaction with the non-stabilised azomethine ylide **A** (derived from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **2**)[8] to give cycloadducts, the spiro(benzo[*d*][1,3]oxazine-4,5'-oxazolidine) derivatives **3**.[7] The cycloadducts **3** proved to be unstable, leading to an unprecedented ring opening-decarboxylation-ring closing cascade sequence to afford 1,3-benzodiazepin-5-ones **4** (Scheme 1).[7]



Scheme 1 1,3-Dipolar cycloaddition reaction of isatoic anhydrides **1** with azomethine ylide **A**.[7]

Given the fascinating reactivity of isatoic anhydrides with azomethine ylide **A**, we sought to expand the scope of this reaction type and identified phthalic anhydride **5a** as a potential carbonyl dipolarophile. Phthalic anhydrides are readily available, inexpensive and versatile raw materials used for the manufacture of a wide range of commercial products including phenolphthalein, anthraquinones and metal phthalocyanines used in the dye industry, polyester polymers and phthalate diesters widely used as plasticizers in flexible PVC products.[9,10] Phthalic anhydrides also undergo a plethora of nucleophilic ring opening reactions of the anhydride ring; however, the carbonyl group acting as a 2π-unit in cycloaddition chemistry has not been recognised in the literature. Recently, transition metal-catalysed decarbonylative cycloadditions of phthalic anhydrides with alkynes, allenes and 1,3-dienes have been reported.[11] We thought that the carbonyl moieties within phthalic anhydride **5a** would be sufficiently activated so as to undergo cycloaddition with azomethine ylide **A** to afford spiro-fused cycloadducts **6a** (Scheme 2).



Scheme 2 Proposed reaction of phthalic anhydrides **5a** with azomethine ylide **A**.

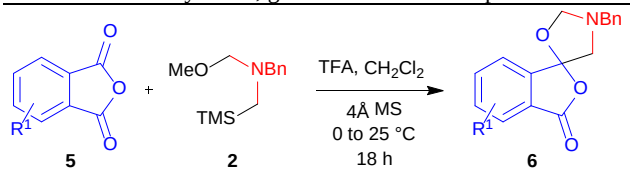
In order to investigate this cycloaddition reaction, phthalic anhydride **5a** was allowed to react with azomethine ylide precursor **2** and 0.05 mole equivalents of trifluoroacetic acid (TFA)[12] in the presence of 4Å molecular sieves. The reaction was essentially complete after 18 h[§] affording the anticipated spiro(isobenzofuranone-oxazolidine) **6a**. Chromatographic purification was required to remove reagent-based impurities. Using silica gel chromatography, the cycloadduct could not be isolated in adequate purity due to decomposition processes that occurred during chromatography, which we assumed was due to the (hydroxylic) acidic nature of the silica gel. Consistent with

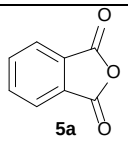
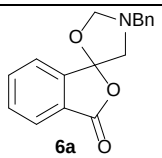
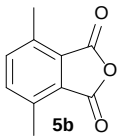
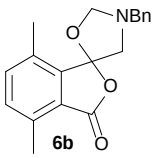
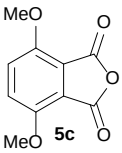
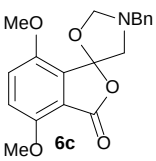
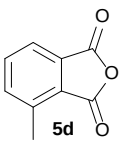
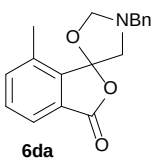
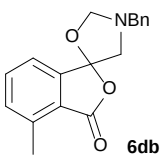
this assumption, when we eluted the crude product through Florisil™, a commercially available less acidic form of silica gel, the crude cycloadduct **6a** was isolated (90% crude yield) with sufficient purity to enable adequate spectroscopic characterisation.[¢] The spectroscopic data was in full accord with oxazolidine **6a** being a mono adduct, with a APCI MS displaying a $[M+H]^+$ ion of m/z 282.1125, ^{13}C NMR displaying 15 signals with one signal at δ168.1 ppm due to the resultant lactone carbonyl carbon. Additionally, the ^1H NMR spectrum displayed separate AB signals at δ4.92 and δ4.85 ppm, and δ3.60 and δ3.45 ppm, assigned to the non-equivalent methylene protons at C2' and C4' of the oxazolidine ring system respectively. The signal at δ4.13 ppm was assigned to the diastereotopic benzylic methylene group. It is worth noting that only the product arising from a single cycloaddition of the azomethine ylide to phthalic anhydride was isolated, which suggests that, under these conditions, the remaining carbonyl group of oxazolidine **6a** was significantly less reactive than the carbonyls of the starting material.

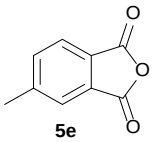
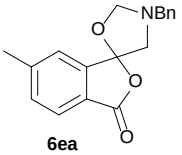
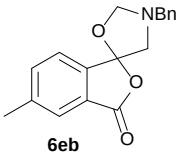
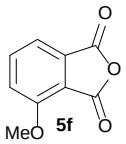
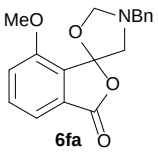
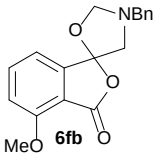
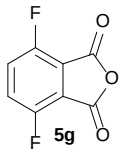
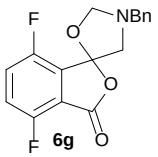
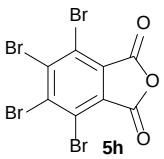
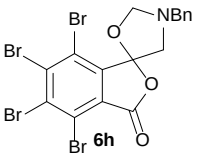
The scope of the reaction was explored by subjecting a range of substituted phthalic anhydrides **5b-h** to the cycloaddition reaction conditions and isolation of the unstable crude products via Florisil™ chromatography (Table 1). The purity of products obtained using this chromatographic technique was adequate for the purpose of spectroscopic characterisation. For phthalic anhydrides **5b-f** substituted with electron-donating groups, such as methyl or methoxy groups, the reaction proceeded to completion and high yields (78->100%) of the corresponding crude spiro(isobenzofuran-1,5'-oxazolidin)-3-ones **6b-f** were obtained (Table 1, entries 2-6). For the symmetrical 3,6-dimethyl or dimethoxy systems **5b** or **5c**, the respective cycloadducts, **6b** or **6c**, were obtained (Table 1, entries 2 and 3). For the unsymmetrical methyl-substituted systems **5d** and **5e**, mixtures of the two respective cycloadducts were obtained (Table 1, entries 4 and 5). 3-Methylphthalic anhydride **5d** furnished the regioisomeric cycloadducts **6da** and **6db** in a ratio of 48:52 (as determined by ^1H NMR analysis) in excellent yield (Table 1, entry 4). When 4-methylphthalic anhydride **5e** was employed, the regioisomeric cycloadducts **6ea** and **6eb** were obtained, again in excellent yield in a ratio of 63:37 (Table 1, entry 5). For both phthalic anhydrides **5d** and **5e** it was necessary to use more of the azomethine ylide precursor **2** (1.5 mole equivalent) and TFA (0.075 mol equiv) to ensure complete consumption of the starting anhydrides. As expected, the unsymmetrical anhydride, 3-methoxyphthalic anhydride **5f**, gave a 30:70 ratio of two regioisomeric cycloadducts **6fa** and **6fb**, obtained in good yield (Table 1, entry 6). It was not possible to separate the mixtures of regioisomeric cycloadducts **6d, 6e** and **6f** due to the instability of the cycloadducts to normal and reverse-phase chromatographic conditions, and lack of separation on Florisil™. Phthalic anhydrides bearing electron-withdrawing groups, 3,6-difluorophthalic anhydride **5g** and 3,4,5,6-tetrabromophthalic anhydride **5h**, were also subjected to the cycloaddition conditions. The reactions proceeded to completion and moderate to high crude yields (67% or 100%) of the corresponding crude spiro(isobenzofuran-1,5'-oxazolidin)-3-ones **6g** or **6h** were obtained (Table 1, entries 7 and 8).

The regioselectivity trends observed for cycloadditions to the unsymmetrical systems **5e-f** are in accord with the cycloaddition being a normal electron demand process and similar to those observed for the cycloadditions of azomethine ylide **A** with isatoic anhydrides.[7] For **5e**, the cycloaddition is less favoured at the carbonyl group *para* to methyl group, consistent with the electron-donating effect of the methyl group reducing the electrophilic character of the *para* carbonyl group to a greater extent that the *meta* carbonyl group. For **5f**, the methoxy group would reduce the reactivity of the *ortho*-related carbonyl group relative to the *meta* carbonyl group by similar electronic effects and possibly additionally by steric hindrance of the incoming dipole at the *ortho* carbonyl group. While the lack of selectivity in the case of **5d** appears anomalous, ^1H NMR analysis of the crude reaction product prior to Florisil™ chromatography, indicated that **6da** and **6db** are formed in a ~1:2 ratio. It appears that in the case of **5d** some losses of the major cycloadduct have occurred during Florisil™ chromatography. This means that the regioselectivity for the cycloaddition of **5d** is actually similar to that of **5f**, which is as expected because of similar stereoelectronic effects.

Table 1 1,3-Dipolar cycloaddition reaction of phthalic anhydrides **5** with azomethine ylide **A**, generated *in situ* from precursor **2**[a]

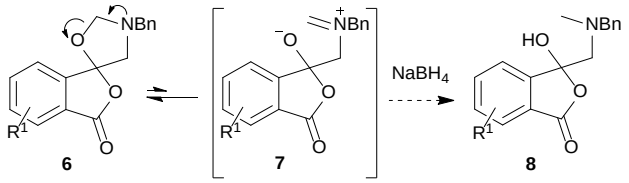


Entry	Anhydride	Product(s)	Ratio of regio-isomers	Crude yield[b] (%)
1	 **5a**	 **6a**		90
2	 **5b**	 **6b**		~100
3	 **5c**	 **6c**		90
4	 **5d**	 **6da**  **6db**	**6da**:**6db** = 48:52	~100

5	 5e	 6ea  6eb	**6ea**:**6eb** = 63:37	88
6	 5f	 6fa  6fb	**6fa**:**6fb** = 30:70	78
7	 5g	 6g		~100
8	 5h	 6h		67

[a] Reaction conditions: **5** (1.0 equiv.), **2** (1.1 equiv.), trifluoroacetic acid (0.05 equiv.), CH_2Cl_2 (7.5 mL/mmol **5**), 4Å molecular sieves, N_2, 0 to 25 °C, 18 h. Column chromatography on Florisil™, eluting with EtOAc.
[b] The cycloadducts are, generally, of limited stability and decompose at ambient temperature/atmosphere. Once isolated (after filtration through Florisil™) they can be stored at 4 °C under an inert atmosphere for up to a day without significant deterioration..

The unstable nature of spiro-isobenzofuran-1,5'-oxazolidin-3-ones **6a-h** is thought to be due to the sensitivity of the contiguous lactone, ketal and hemiaminal ether moieties to Brönsted or Lewis acids. Reductive ring-opening of the hemiaminal ether moiety within oxazolidines has been reported,[13] and can occur by activation of the C-O bond through coordination to the oxygen atom of a reducing agent with Lewis acid properties (e.g., BH_3), C-O bond fission to form an acyclic iminium ion intermediate, and reduction of this species by hydride ion. We postulated that a relatively slow ring-opening of oxazolidine **6** to give iminium ion **7** would occur,[7,14] and then reduction with sodium borohydride would form the corresponding 1-(*3H*)-isobenzofuranones **8**, which we hoped would be sufficiently stable to be isolated in high purity so as to allow chromatographic separation (Scheme 3). In the cases where mixtures of regioisomeric cycloadducts **6** were subjected to these conditions, we anticipated that the resultant regioisomeric isobenzofuranones **8** would be obtained, and if separable, would provide more robust validation of the assigned structures.



Scheme 3 Proposed ring-opening of oxazolidines **6** with sodium borohydride.

In order to investigate this reductive ring-opening reaction, spiro-fused oxazolidine **6a** was treated with sodium borohydride (1.5 mole equivalent) in methanol, and after four hours at ambient temperature 1-(*3H*)-isobenzofuranone **8a** was isolated in 76% yield after purification by silica gel chromatography (Table 2, Entry 1). As far as we are aware, this is the first report describing the synthesis of this type of functionalised 1(*3H*)-isobenzofuranone,[15] although the chemistry of 3-hydroxyisobenzofuranones (3-hydroxyphthalides) is of much interest, particularly as this moiety is found in natural products and is used as starting materials for the synthesis of bioactive compounds.[15-17] The analytical and spectroscopic data obtained for the product was in full accord with the proposed structure of compound **8a**; the ASAP high resolution MS showed a $[M+H]^+$ ion at m/z 282.1283, consistent with addition of two hydrogens to **6a**, the ^{13}C NMR spectrum showed a resonance at δ168.5 ppm assigned to the carbonyl group of the lactone ring and the ^1H NMR spectrum displayed three resonances at δ3.82, 2.93 and 2.55 ppm, which were assigned to the protons at the benzylic methylene group, the methylene group between the quaternary carbon centre and the nitrogen atom, and the *N*-methyl group, respectively. Further evidence of the structure of 1(*3H*)-isobenzofuranone **8a** was provided by HMBC spectroscopy, which displayed two diagnostic cross-peaks associated with three-bond correlations (J^3) between the *N*-methyl carbon atom (C_j) and both sets of methylene group protons (H_i and H_k) (Fig. 1).

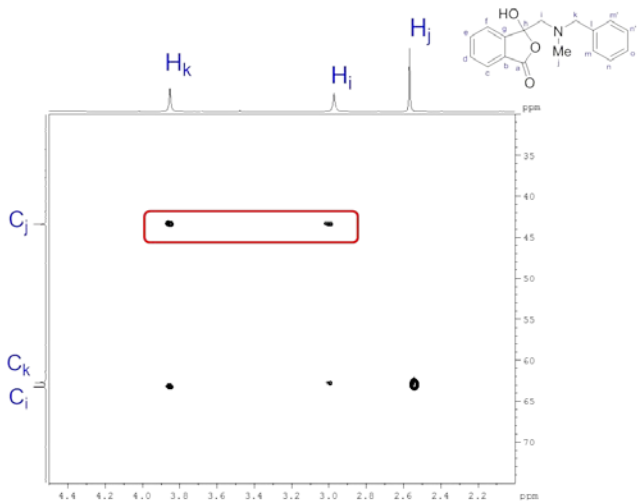


Fig. 1 Section of the HMBC spectrum contour plot of **8a**; the three-bond correlations of interest are highlighted.

The scope of the reductive ring-opening process was explored by treating crude spiro-isobenzofuran-1,5'-oxazolidin-3-ones **6b-h**, isolated after chromatography on Florisil™, with sodium borohydride in methanol (Table 2, entries 2-8). The 4,7-dimethyl-spiro-isobenzofuran-1,5'-oxazolidin-3-one **6b** underwent reductive ring-opening smoothly to afford the corresponding 1(3*H*)-isobenzofuranone **8b** in 69% yield (Table 2, entry 2). Whereas the two sets of diastereotopic methylene protons in the *N*-benzyl(methyl)aminomethyl side-chain of **8a** exhibited as two singlets in the ^{1}H NMR spectrum, the corresponding protons in **8b** exhibited as four geminally coupled doublets in the ^{1}H NMR spectrum.[‖]

The different spectral phenomena of **8a** and **8b** raised some concerns about the structural assignment of **8b**. Fortunately, compound **8b** was a highly crystalline solid amenable to analysis by single crystal X-ray crystallography analysis (Fig. 2). The structure exhibits an anomeric effect at the C8 hemiacetal centre and the O-H forms a weak O-H···N intramolecular hydrogen bond between O3 and N1 ((O···N = 2.6577(10) Å, O-H···N 128.5(14)°). As a result of this hydrogen bond the conformation about the C8-O3 bond allows for effective overlap between a lone pair on O3 with the σ* C-O antibonding orbital for the C8-O2 bond. In turn this interaction results in shortening of the C8-O3 bond distance (1.383(1) Å) and lengthening of the C8-O2 bond distance (1.477(1) Å), when compared to reported structures when this interaction is absent (mean bond length of 1.424 Å and 1.463 Å respectively).[¥] The anomeric effect is likely to be enhanced to a small degree by the formation of the intramolecular O-H···N hydrogen bond, a phenomenon that has been reported previously.[18]

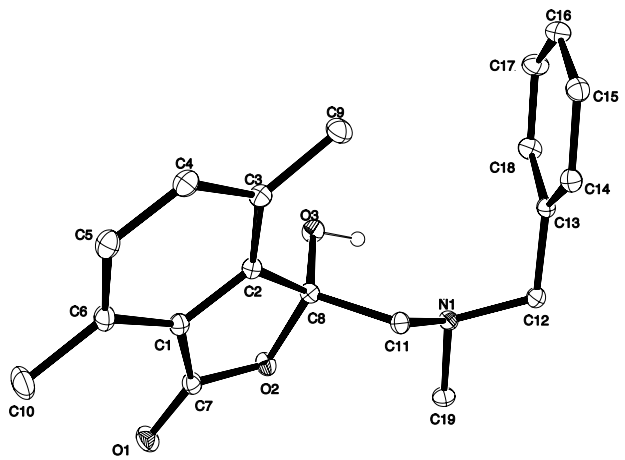


Fig. 2 Single crystal X-ray structure of 1(3*H*)-isobenzofuranone **8b**.[¶]

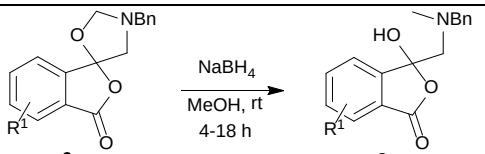
The anomeric effect observed in the crystal structure of **8b** suggests the possibility of equilibrium between this ring-closed form and a ring-opened ammonium-keto-carboxylate form in the solution state. Such an equilibrium would enable interconversion of the diastereotopic methylene hydrogens and could explain the differing NMR spectral phenomena observed for lactones **8a** and **8b**. Alternatively, the signals observed for the diastereotopic protons of **8a** could be caused by rapid rotation of the less-hindered side-chain relative to **8b** and coalescence of signals of the conformations involved. Further studies are required to elucidate the source of the ^{1}H NMR phenomena observed for the side-chains methylene protons of **8a** and **8b**.

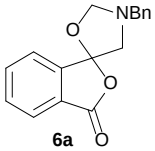
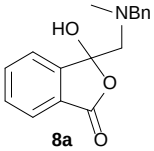
For 4,7-dimethoxy-spiro-(isobenzofuran-1,5'-oxazolidin)-3-one **6c**, the reductive ring-opening with sodium borohydride proceeded to give the corresponding 1(3*H*)-isobenzofuranone **8c**, which was obtained in pure form in a 35% yield (Table 2, entry 3).

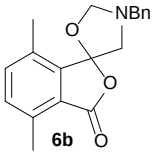
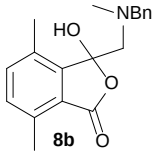
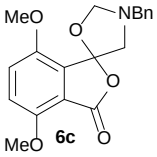
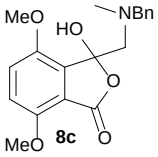
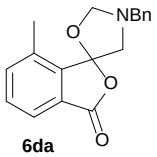
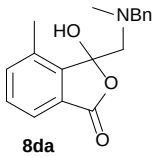
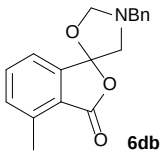
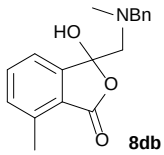
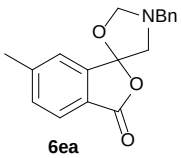
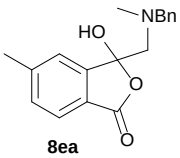
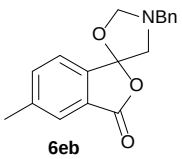
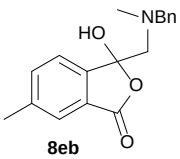
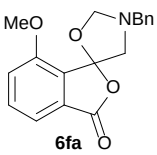
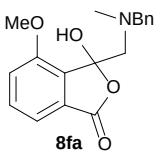
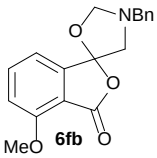
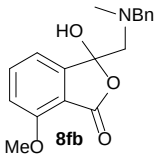
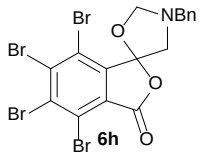
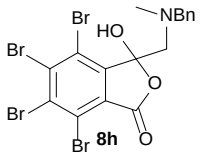
The oxazolidines obtained as mixtures of regioisomers were all reduced to the corresponding mixture of separable isobenzofuranones. The regioisomeric mixture of **6da** and **6db** underwent reductive ring-opening to afford a corresponding regioisomeric mixture of 1(3*H*)-isobenzofuranones **8da** and **8db**. The regioisomers were separated by chromatography to give **8da** (31% yield) and **8db** (31% yield) representing a combined isolated yield of 62% for the regioisomers (Table 2, entry 4). The structures of **8da** and **8db** were confirmed by ^{1}H, ^{13}C and 2D NMR experiments, and HRMS. In a similar manner, reductive ring-opening of regioisomeric mixture **6ea** and **6eb** afforded, after chromatographic purification, the 1(3*H*)-isobenzofuranones **8ea** (29%) and **8eb** (14%), representing a modest total overall yield of 43% (Table 2, entry 5). The regioisomeric mixture **6fa** and **6fb** afforded 1(3*H*)-isobenzofuranones **8fa** (20%) and **8fb** (26%), representing a combined yield of 46% (Table 2, entry 6). Although each of these reduction reactions were judged to be complete by TLC and ^{1}H NMR analysis, the poor to modest isolated yields in some cases is attributed to the difficulty in separating the products by chromatography.

A reaction with a starting material substituted with electron-withdrawing groups was less selective leading to lower yields of the expected isobenzofuranone. The 4,5,6,7-tetrabromo-spiro-(isobenzofuran-1,5'-oxazolidin)-3-one **6h** underwent reductive ring-opening to afford the corresponding 1(3*H*)-isobenzofuranone **8h**, in only 12% yield (Table 2, entry 7). The low yield in this case was a combination of less selective reduction processes/over reduction that led to complex mixtures and the resultant difficulty in chromatographic separation of the pure product from other product contaminants during chromatography.

Table 2



Entry	Substrate (s)	Isobenzofuranone	Yield (%)[a]
1			68

2	 **6b**	 **8b**	69
3	 **6c**	 **8c**	35
4	 **6da**	 **8da**	31
	 **6db**	 **8db**	31
5	 **6ea**	 **8ea**	29
	 **6eb**	 **8eb**	14
6	 **6fa**	 **8fa**	20
	 **6fb**	 **8fb**	26
7	 **6h**	 **8h**	12

[a] Reaction conditions: oxazolidine **6** (1.0 equiv.), $NaBH_4$ (1.50 equiv.), MeOH (6.0 mL/mmol **6**), 25 °C, N_2, 1-18 h.

Conclusions

The ability of the phthalic anhydride carbonyl group to act as a 2π component in cycloaddition reactions has been demonstrated, namely in dipolar cycloaddition reactions with azomethine ylides. The product spiro(isobenzofuran-oxazolidin-3-one derivatives can be isolated in crude form via chromatography on Florisil™, and in turn selectively reduced with sodium borohydride to afford functionalised isobenzofuranone derivatives. Further derivatisation of the products is possible via deprotection of the *N*-Bn group or by switching the *N*-Bn group in the azomethine ylide to *N*-allyl or other *N*-R groups, thus expanding the utility of this method.[19] Future work will be directed towards further harnessing the inherent reactivity of the spiro(isobenzofuran-oxazolidin-3-one derivatives and synthetic applications of the isobenzofuranone derivatives.

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Notes and references

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† This paper is dedicated to Professor Ei-ichi Negishi on the occasion of his 80th birthday.

‡Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data of new compounds, X-ray crystallographic data for **8b** (CIF) and CCDC searches. Summary of reaction optimisation of cycloaddition chemistry. See DOI: 10.1039/b000000x/

§ 96% conversion of starting phthalic anhydride **5a** as determined by ^{1}H NMR analysis of the reaction mixture.

¢ Oxazolidine **6a** decomposes under a range of conditions, including during silica chromatography, in the presence of excess trifluoroacetic acid, or when dissolved in water-methanol mixtures.

‖A range of fluxional behaviour was observed for the diastereotopic methylene protons in the side-chains of isobenzofuranones **8**. Typically, the diasterotopic protons in the products with a benzo substituent adjacent to the furanone ring (**8b-d**, **f** and **h**) exhibited as four distinct signals in the ^{1}H NMR time-scale, whereas for products without substituents adjacent to the furanone ring (**8a** and **8e**) the diasterotopic protons exhibited as two distinct signals.

¶Single crystals of 1(3*H*)-isobenzofuranone **8b** were obtained by recrystallisation from dichloromethane/pentane, mounted in inert oil and transferred to the cold gas stream of the diffractometer. **Crystal data.** $C_{19}H_{21}NO_3$, M = 311.37, T = 130.0(2) K, λ = 0.71073 Å, Monoclinic, space group $P2_1/c$ a = 7.2941(2), b = 13.2249(3), c = 17.2264(4) Å, β= 96.919(2)° V = 1649.62(7) Å^3, Z = 4, D_c = 1.254 Mg M^{-3} μ(Mo-Kα) = 0.085 mm^{-1}, *F(000)* = 664, crystal size 0.49 x 0.38 x 0.29 mm. θ_{max} = 36.5°, 45689 reflections measured, 7831 independent reflections (R_{int} = 0.034) the final R = 0.0461 [I > 2σ(I), 6084 data] and $wR(F^2)$ = 0.10369 (all data) GOOF = 1.073. CCDC deposit code: 1047327.

¥The CCDC was searched for structures containing fragments that lacked the anomeric effect. The mean bond length was obtained from structures with R < 5% (see ESI).

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