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1,3-Dipolar Cycloaddition−Decarboxylation Reactions of an Azomethine Ylide with Isatoic Anhydrides: Formation of Novel Benzodiazepinones

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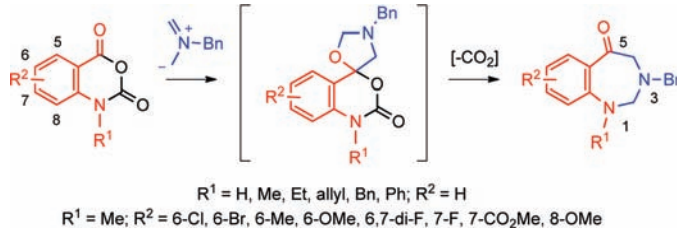
ABSTRACT



A nonstabilized azomethine ylide reacts with a wide range of substituted isatoic anhydrides to afford novel 1,3-benzodiazepin-5-one derivatives, which are generally isolated in high yield. The transformations involve 1,3-dipolar cycloaddition reactions of the ylide with the anhydrides to give transient, and in a representative case spectroscopically observable, oxazolidine intermediates that undergo ring-opening−decarboxylation−ring-closing reaction cascades to yield the 1,3-benzodiazepin-5-one products.

The 1,3-dipolar cycloaddition reaction[1] of azomethine ylides with dipolarophiles is an efficient and versatile method for the construction of five-membered heterocycles.[2] The majority of research into azomethine ylide cycloaddition chemistry has focused on the use of alkenes as dipolarophiles for the synthesis of pyrrolidine-containing molecules of biological[3] or materials science interest.[4] A range of hetero multiple bonded systems, including carbonyl, thiocarbonyl, isothiocyanato, imino, isocyanato, nitrile, nitroso, and azo derivatives, also act as azomethine ylide dipolarophiles.[5] In the case of carbonyl dipolarophiles, aldehydes and ketones readily undergo cycloaddition reactions with azomethine ylides,[6] whereas carboxyl moieties (e.g., carboxylic acids and esters) are generally unreactive in such reactions.[6d] The relative lack of reactivity of the carbonyl group of carboxyl

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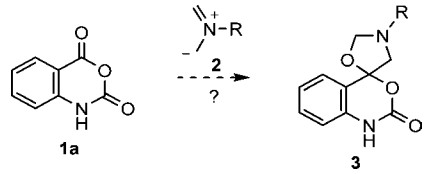
compounds compared with that of aldehydes can be explained by frontier molecular orbital theory.[7,8]

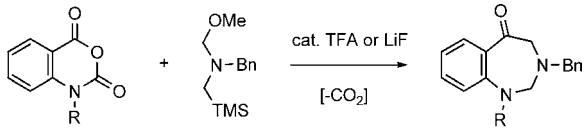
Isatoic anhydride **1a** was identified as a potential new carbonyl dipolarophile. Isatoic anhydride derivatives are readily available,[9] versatile synthetic intermediates undergoing reactions with a broad range of nucleophiles to afford 2-aminobenzoyl derivatives.[10] Thus, it was thought that the C4-carbonyl moiety within isatoic anhydride **1a** may be sufficiently activated that it would undergo cycloaddition with an azomethine ylide **2** to afford the spiro-fused oxazolidine **3** (Scheme 1).

Scheme 1. Proposed Reaction of Isatoic Anhydride with an Azomethine Ylide



In order to test this hypothesis, isatoic anhydride **1a** was allowed to react with azomethine ylide **2a** (R = Bn), formed from *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzylamine **4**[11] and 0.05 mol equiv of trifluoroacetic acid (TFA)[12] in the presence of 4 Å molecular sieves. To our surprise, the benzodiazepinone **5a**, rather than the anticipated spiro-fused cycloadduct **3** (R = Bn), was isolated as a single major product in moderate yield (Table 1, entry 1). The analytical and spectroscopic data for the product were in full accord with a novel 1,3-benzodiazepin-5-one ring system, and the structural assignment was confirmed by single crystal X-ray crystallographic analysis (Figure 1).[13]

Table 1. Transformation of Isatoic Anhydride and *N*-Functionalized Isatoic Anhydrides into 1,3-Benzodiazepin-5-ones



entry	1	R	cond[a]	time (h)	yield (%)[b]
1	**a**	H	A	24	42
2	**b**	Me	A	36	92
3	**c**	Et	A	16	79
4	**d**	Allyl	A	16	71
5	**e**	Bn	A	40	77
6	**f**	Ph	A	16	80
7	**a**	H	B	3	0
8	**b**	Me	B	6	88
9	**c**	Et	B	2	96
10	**d**	Allyl	B	4	76
11	**e**	Bn	B	3	100
12	**f**	Ph	B	12	90

[a] Reaction conditions, A: **4** (1.8 equiv), 4 Å molecular sieves, TFA (0.05 equiv), CH_2Cl_2, 0 °C to rt; B: **4** (1.8 equiv), 4 Å molecular sieves, LiF (1.25 equiv), CH_3CN, sonication, 35 °C. [b] Yield of product isolated after chromatography and/or crystallization.

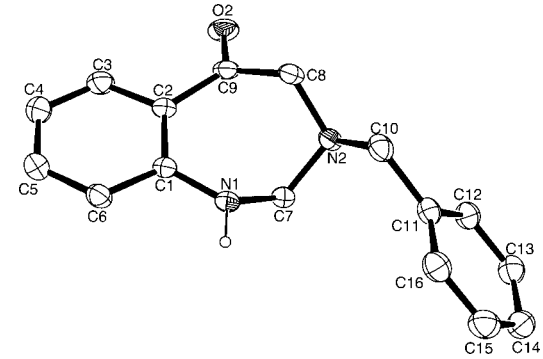


Figure 1. Single crystal X-ray structure of benzodiazepinone **5a**.

The scope of this novel reaction was explored by subjecting *N*-substituted isatoic anhydride derivatives to the cycloaddition reaction conditions. The derivatives **1b**−**f**, substituted on nitrogen with alkyl, allyl, benzyl, and phenyl groups, were readily prepared from isatoic anhydride **1a**.[14,15] Reaction of the isatoic anhydrides **1b**−**f** with the azomethine ylide **2a** resulted in the corresponding *N*-substituted 1,3-benzodiazepin-5-ones **5b**−**f** respectively, which were isolated in 71−92% yield (Table 1, entries 2−6). The higher yields obtained for the *N*-substituted derivatives **5b**−**f**, versus the parent system **5a**, was attributed to a combination of cleaner reactions, as evidenced by NMR analyses of the crude reaction products, and the greater stability of the *N*-substituted products toward chromatographic purification.

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(13) Crystallographic data (CIF) for the structure reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre (CCDC) and allocated the deposition number CCDC-796928 for compound **5a**. A copy of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 IEZ, UK; fax: (44) 01223 336 033; email: deposit@ccdc.cam.ac.uk.

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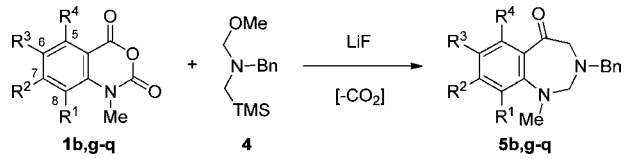
Alternative conditions (amine reagent **4** and LiF with sonication at 35 °C) have been developed by Padwa[16] for the generation of the azomethine ylide **2a**. When the parent system **1a** was reacted under these conditions, a complex product mixture resulted, with no evidence of starting material **1a** or 1,3-benzodiazepin-5-one **5a** (Table 1, entry 7). In contrast, under these conditions, the *N*-substituted isatoic anhydrides **1b**−**f** resulted in high yields of the 1,3-benzodiazepin-5-ones **5b**−**f** (Table 1, entries 8−12). The lack of isolation of **5a** from the reaction promoted by LiF was attributed to a higher level of side reactions and/or the sensitivity of **5a** toward degradation under these conditions.

In order to study the effect of varying isatoic anhydride aromatic substituents on the outcome of this process, a series of *N*-methyl benzo-substituted isatoic anhydrides **1g**−**q** was prepared[14] and subjected to the LiF-promoted reaction conditions. For isatoic anhydrides substituted with electron-withdrawing groups, such as fluoro, chloro, bromo, and methoxycarbonyl groups, the reaction proceeded to completion and high yields of the 1,3-benzodiazepin-5-one products were obtained (Table 2, entries 3, 4, 7, 8, and 10). For isatoic anhydrides substituted with electron-donating groups, reactions did proceed when the groups were *meta* to the carbonyl group [**1g** (8-methoxy), **1k** (6-methyl), and **1n** (6-methoxy); entries 2, 6, and 9] but were incomplete for the 6-substituted examples. The high yield of product obtained for the 8-methoxy example **1g** demonstrated that a substituent *ortho* to the isatoic anhydride nitrogen does not hinder the reaction. For isatoic anhydrides substituted with electron-donating groups *ortho* or *para* to the C4-carbonyl group, no reaction occurred with starting material being recovered in high yield [**1j** (7-methoxy), **1p** (5-methyl), and **1q** (6,7-dimethoxy); entries 5, 11, and 12]. The lack of reactivity in these cases indicates that *ortho* or *para* electron-donating groups can deactivate the carbonyl group toward reaction with the azomethine ylide.[17] In the case of the 5-methyl derivative **1p**, the steric bulk of the methyl group may also hinder the reaction.

Table 2. Transformation of Benzo-Substituted *N*-Methyl Isatoic Anhydrides into 1,3-Benzodiazepin-5-ones[a]

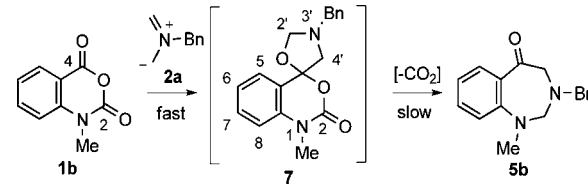


entry	**1**	R^1	R^2	R^3	R^4	time (h)	yield (%)[b]
1	**b**	H	H	H	H	6	88
2	**g**	OMe	H	H	H	3	80
3	**h**	H	F	H	H	24	66
4	**i**	H	CO_2Me	H	H	1.5	94
5	**j**	H	OMe	H	H	48	0[c]
6	**k**	H	H	Me	H	24	66[d]
7	**l**	H	H	Cl	H	3	76
8	**m**	H	H	Br	H	2	63
9	**n**	H	H	OMe	H	41	46[e]
10	**o**	H	F	F	H	6	93
11	**p**	H	H	H	Me	24	0[f]
12	**q**	H	OMe	OMe	H	56	0[g]

[a] Reaction conditions: **4** (1.8 equiv), 4 Å molecular sieves, LiF (1.25 equiv), CH_3CN, 35 °C, sonication. [b] Yield of product isolated after chromatography and/or crystallization. [c] 73% of starting material **1j** was recovered. [d] 13% of starting material **1k** was recovered. [e] 36% of starting material **1n** was recovered. [f] 79% of starting material **1p** was recovered. [g] 77% of starting material **1q** was recovered.

In an effort to observe a reaction intermediate analogous to **3**, the reaction of *N*-methyl isatoic anhydride **1b** with azomethine ylide **2a** was followed by ^{1}H NMR and IR spectroscopy. For the NMR study, a solution of **1b** and reagent **4** (in CD_2Cl_2 at 25 °C) was treated with TFA and spectra were recorded over a 24 h period. It was observed that signals due to **1b** were rapidly replaced by signals due to a transient oxazolidine intermediate **7**, with the conversion being complete after *ca.* 20 min (Scheme 2).[18,19] Particularly

Scheme 2. NMR and IR Spectroscopic Observation of Oxazolidine Intermediate **7**



diagnostic features of the ^{1}H NMR spectrum of intermediate **7** were the geminally coupled doublets at δ 4.82 and 4.69 ppm assigned to the nonequivalent oxazolidine methylene protons H2′a and H2′b. At this time, signals due to the end-product benzodiazepinone **5b** were not apparent. However, after this time, the signals due to the oxazolidine intermediate **7** were slowly replaced with those of **5b**, with the full conversion complete after 24 h.

Isatoic anhydride **1b** exhibits two strong carbonyl stretches at $\nu_{C=O}$ 1780 and 1730 cm^{-1} assigned to the C4 and the C2 carbonyl groups, respectively. The IR spectrum of the reaction mixture containing the oxazolidine intermediate **7** showed a single new strong carbonyl stretch at $\nu_{C=O}$ 1725 cm^{-1}. After a 24 h period, the carbonyl stretch at 1725 cm^{-1} gave way to a carbonyl stretch at $\nu_{C=O}$ 1654 cm^{-1} due to the end product 1,3-benzodiazepin-5-one **5b**.

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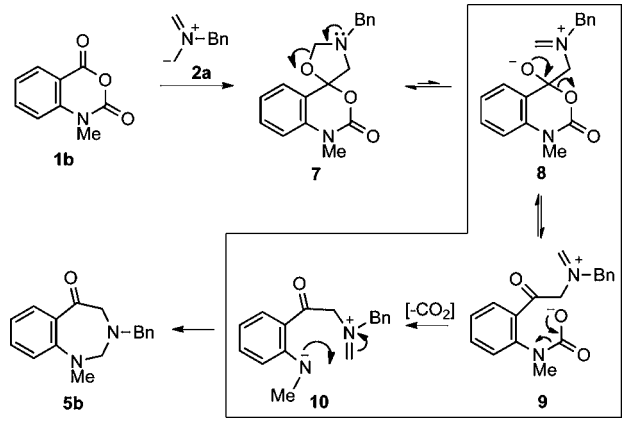
(17) This result is in contrast to cycloaddition reactions of azomethine ylide **2a** with benzaldehydes which appear to be unaffected by substitution with electron-donating groups (see ref 6d).

(18) The ^{1}H NMR spectra of **7** were complicated due to side reactions of the azomethine ylide **2a** and/or precursor **4**. The signals due to **7** were identified by subtraction of the side product signals observed during a control experiment performed without isatoic anhydride **1b**. Selected data for **7**: $\nu_{C=O}$ ($CDCl_3$) 1725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 − 7.17 (m, 7H), 7.16 (dd, J = 7.6, 6.8 Hz, 1H, H6), 6.99 (d, J = 8.2 Hz, 1H, H8), 4.82 (d, J = 5.6 Hz, 1H, H2′a), 4.69 (d, J = 5.6 Hz, 1H, H2′b), 4.07 − 3.99 (m, 2H, CH_2Ph), 3.53 (s, 2H, N4′), 3.38 (s, 3H, N1Me).

(19) The instability of intermediate **7** has so far prevented its purification.

A plausible mechanism for the transformation of isatoic anhydride **1b** into 1,3-benzodiazepin-5-one **5b** is shown in Scheme 3. A rapid 1,3-dipolar cycloaddition reaction of the azomethine ylide **2a** with the benzoyl-like carbonyl group of the isatoic anhydride **1b** results in the spectroscopically observed oxazolidine intermediate **7**. A cascade process then occurs, initiated by a relatively slow ring opening of oxazolidine **7** to give the iminium ion **8**.[20] The alkoxide **8** then ring opens to give ketone **9**, which then decarboxylates to provide amide ion **10**.[21,22] A 7-*endo-trig* ring closure[23] of the amido-iminium species **10** then affords the isolated 1,3-benzodiazepin-5-one **5b**.

Scheme 3. Plausible Mechanism for the Transformation of Isatoic Anhydrides into 1,3-Benzodiazepin-5-ones



This paper describes *the first report of cycloaddition chemistry of the activated carbonyl group within isatoic anhydride derivatives.* The framework of the 1,3-benzodiazepin-5-one products **5** is novel, and analogues are readily available. The framework of **5** bears a close relationship to that of benzoazepine and benzodiazepine drugs, e.g. Diazepam, that are known as privileged structures in pharmaceutical discovery.[24] Further studies will be aimed at expansion of the scope of the chemistry through exploring alternative dipoles or activated carboxyl groups and at application of the 1,3-benzodiazepin-5-one framework in bioactive discovery.

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Supporting Information Available: Experimental procedures and compound characterization for compounds **1o**, **5a**−**i**,**k**−**o**. ^{1}H NMR and IR spectra for intermediate **7**. X-ray structural data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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