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Diels–Alder cycloadditions of 3-phenylamino-5-bromo-2-pyrone for the synthesis of constrained α-amino acid derivatives

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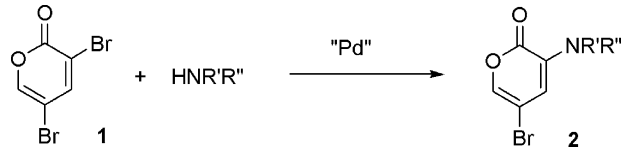
Abstract—3-Phenylamino-5-bromo-2-pyrone undergoes facile Diels–Alder cycloadditions with various electron deficient dienophiles to afford an array of functionally rich and stereochemically defined cycloadducts in good to excellent isolated yields. Due to the electron donacity of the amine group, it only proceeds in normal electron demand D–A cycloadditions. Subsequent ring openings with NaOMe provided constrained α-amino acid derivatives.

Present in a number of naturally occurring products,[1] 2-pyrone units are versatile synthetic building blocks that can be used for the synthesis of various structurally and physiologically important molecules, primarily through Diels–Alder cycloadditions with suitable dienophiles.[2] Also interested are the 2-pyrones themselves, as some of the 2-pyrones with hydroxyl, alkenyl, aryl, and alkyl groups at C4 position were reported to be biologically active.[3]

In connection to our ongoing research program on 3,5-dibromo-2-pyrone,[4] we have previously reported it can undergo the Sonogashira and Stille coupling reactions, regioselectively at C3–Br position.[4a–d] The resulting Stille and Sonogashira coupling products were shown to have potent ambident dienyl character, capable of undergoing either normal and inverse electron demand Diels–Alder cycloadditions.[4b–d] Also reported were its Pd-catalyzed amination reactions with various aryl- and alkylamines affording a series of 3-aryl- and alkylamino-5-bromo-2-pyrones (Scheme 1).[5]

The amino-substituted 2-pyrones are of particular interest as they can be used as synthetic building blocks for various constrained carbocyclic α-amino acids upon



Scheme 1. Pd-catalyzed aminations of 3,5-dibromo-2-pyrone.

Diels–Alder cycloadditions with appropriate dienophiles. As shown previously in a number of reports, conformationally constrained carbocyclic α-amino acids have various important biological properties.[6] The substituent on the 2-pyrone ring often plays a key role in the enzymatic interactions. They have also been incorporated into peptides for the generation of structurally defined peptides as various conformational probes and biological agents.[7]

In this account, we wish to report on the generation of various carbocyclic α-amino acid derivatives from 3-phenylamino-5-bromo-2-pyrone through the cycloadditions and subsequent lactone ring openings.

Due to the presence of the amino group on the 2-pyrone unit, 3-phenylamino-5-bromo-2-pyrone underwent only normal electron demand D–A cycloadditions with electron deficient dienophiles (Table 1). Attempted Diels–Alder cycloadditions with electron rich dienophiles, for example, benzyl vinyl ether, gave only a trace of cycloadducts even after prolonged heating at 100 °C.

Keywords: Diels–Alder; 2-Pyrone; Constrained α-amino acid.
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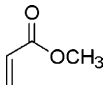
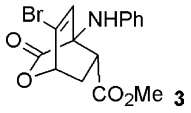
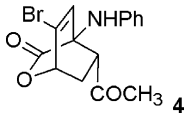
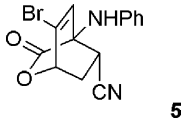
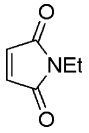
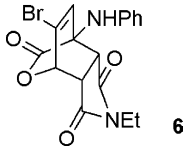
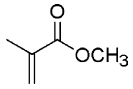
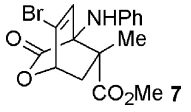
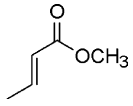
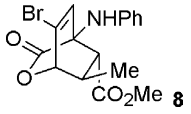
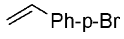
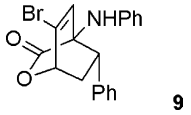
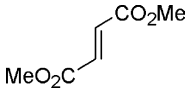
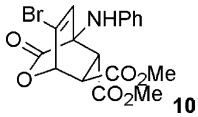
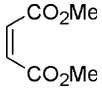
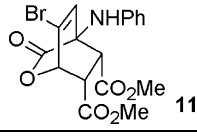
Table 1. D–A cycloadditions with various electron deficient dienophiles.[8]

Entry	Dienophile	Time	*exo*-Adduct	*endo*/*exo* (**a**/**b**)	Yield (%)
1		0.5 h	 **3**	47:53	95
2		0.5 h	 **4**	18:82	85
3		1.5 h	 **5**	53:47	81
4		0.5 h	 **6**	44:56	84
5		1 d	 **7**	48:52	84
6		3 d	 **8**	46:54	80
7		2 h	 **9**	76:24	83
8		1 d	 **10**	10:90	81
9		1 d	 **11**	30:70	84

Addition of Lewis acids gave no significant improvements.[4c] Unlike the parent 3,5-dibromo-2-pyrone or other 2-pyrone derivatives, the Diels–Alder cycloadditions of 3-phenylamino-5-bromo-2-pyrone exhibited moderate to high *exo*-selectivity. The presence of aryl group may impose an additional steric repulsion with the incoming dienophile to destabilize the otherwise favorable *endo*-transition state. The reactions are faster than the parent 3,5-dibromo-2-pyrone,[4e] due to the strong electron donacity of the amino group. Noteworthy is that the cycloaddition with dimethylmaleate proceeds in a concerted fashion, to provide the *cis*-disubstituted cycloadduct (entry 8). The cycloaddition of the parent 3,5-dibromo-2-pyrone with the same dienophile proceeded in a stepwise manner to produce *trans*-disubstituted cycloadducts, presumably due to the steric congestion in both *endo*- and *exo*-transition states as reported earlier.[4e] CH_2Cl_2 turned out to be much better than toluene, in terms of both reaction rates and product yields.

The stereochemistry of the *endo*- and *exo*-cycloadduct is generally assigned by the chemical shift of the proton at C5 of the cycloadducts.[4e] Because of the anisotropic shielding effect of the olefin bridge, the *endo*-H (in *exo*-cycloadduct) normally appears at higher field than the

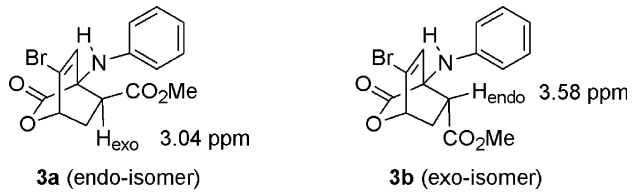


Figure 1. ^{1}H NMR chemical shifts of H_{endo} and H_{exo}.

exo-H. Unlike the analogous cases, however, the *endo*-Hs of the products in Table 1 are shown at lower field than the *exo*-Hs. The unusual downfield shift of the *endo*-H is believed to be due to the anisotropic deshielding effect of the neighboring phenyl group. A simple computer modeling study suggests that H_{endo} would indeed lie in the deshielding zone of phenyl ring (Fig. 1).

Lactone ring opening of the cycloadducts with NaOMe would provide various substituted carbocyclic amino acid methyl esters. While the *endo*-adducts readily underwent ring-opening reactions, the *exo*-adducts did not, due to the steric hindrance of the dangling *exo*-substituents. The treatment of various *endo*-cycloadducts with NaOMe in MeOH at 0 °C provided the corresponding α-amino acid methyl esters (Table 2).[9] The ring-opening reactions at rt, in most cases, provided aromatized products.

In entry 2, the initially formed ring-opening product further underwent an aldol-type condensation to the bicyclic product **4c**.

The ring-opening reactions of the *exo*-cycloadducts were not expected to proceed as smoothly as those of the

Table 2. Lactone ring opening of the *endo*-adducts

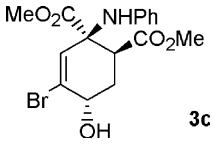
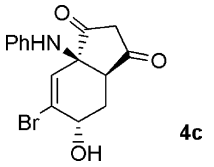
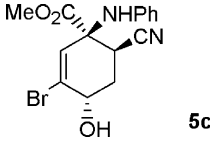
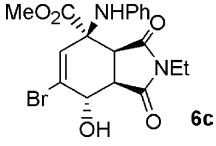
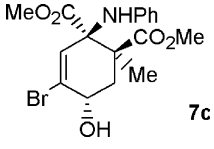
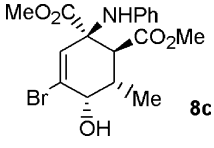
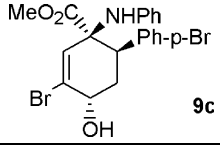
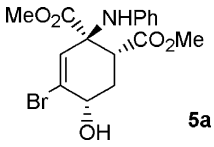
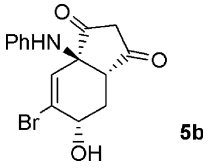
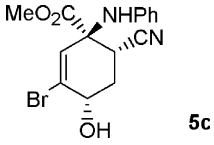
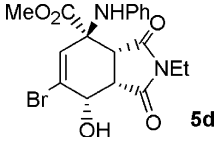
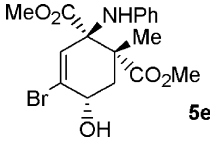
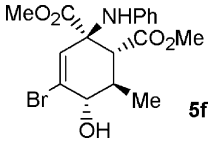
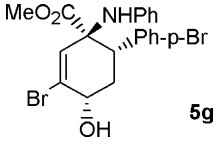
Entry	Cycloadduct	Time	Amino acid	Yield (%)
1	**3a**	0.5 h	 **3c**	90
2	**4a**	5 min	 **4c**	75
3	**5a**	2 h	 **5c**	93
4	**6a**	5 min	 **6c**	89
5	**7a**	12 h	 **7c**	95
6	**8a**	5 min	 **8c**	90
7	**9a**	5 min	 **9c**	89

Table 3. Lactone ring opening of the *exo*-cycloadducts

Entry	Cycloadduct	Time	Amino acid	Yield (%)
1	**3b**	2 h	 **5a**	99
2	**4b**	5 min	 **5b**	79
3	**5b**	5 min	 **5c**	89
4	**6b**	2 h[a]	 **5d**	83
5	**7b**	12 h	 **5e**	85
6	**8b**	2 h	 **5f**	92
7	**9b**	3 h	 **5g**	90

[a] The addition of NaOMe was made at −78 °C.

endo-ones. The *exo*-substituents on the bicyclolactones would sterically block the incoming nucleophiles as shown in analogous cases. Nevertheless, the *exo*-adducts underwent quite nice ring-opening reactions (Table 3).

The attempted ring-opening reactions of **10** and **11** gave more than a few unidentifiable base-line spots. Other 3-arylamino-5-bromo-2-pyrones also undergo facile normal electron demand D–A cycloadditions (data not shown). The cycloadditions of 3-alkylamino-5-bromo-2-pyrones were not feasible due to their thermal instability.

In summary, we have found that 3-phenylamino-5-bromo-2-pyrone undergoes facile Diels–Alder cycloadditions faster than the parent 3,5-dibromo-2-pyrone, owing to the electron donating phenylamino group at C3 position, to furnish an array of functionally rich bicyclolactones in good to excellent yields. The steric hindrance between the phenylamino group and incoming dienophile in the *endo*-TS may account for the observed preference of the *exo*-cycloadduct. The resulting cycloadducts were readily converted into a series of conformationally constrained α-amino acid derivatives.

Acknowledgements

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8. Representative procedure: A mixture of 50 mg (0.19 mmol) of 3-phenylamino-5-dibromo-2-pyrone and 48 mg (3 equiv) of methyl acrylate in 3 mL of CH_2Cl_2 was heated at 100 °C in a sealed tube for 30 min. The reaction mixture was cooled to rt, concentrated, and chromatographed to give 30 mg of the *endo* (**3a**) and 33 mg of the *exo* cycloadduct (**3b**), in 45% and 50% yield, respectively.
9. Representative procedure: To a flask charged with 20 mg (0.06 mmol) of **3a** were added 3 mL of anhydrous MeOH and 0.03 mL of NaOMe (28% in MeOH) at 0 °C. After 30 min at 0 °C, the reaction mixture was acidified to pH 5 by adding 1 M HCl (aq), and partitioned into CH_2Cl_2 and H_2O. The separated organic solution was dried over $MgSO_4$, filtered, concentrated, and chromatographed (hexanes/EtOAc = 4:1) to provide 20 mg of **5a** in 90% yield.