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Regioselective Synthesis of Tetrasubstituted Pyrroles by 1,3-Dipolar Cycloaddition and Spontaneous Decarboxylation

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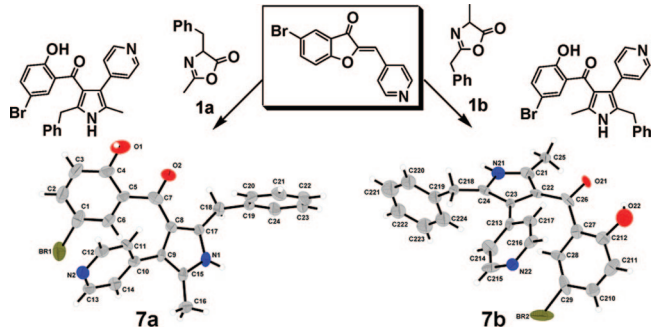
ABSTRACT



We developed a novel regioselective synthesis of tetrasubstituted pyrroles via the classic 1,3-dipolar cycloaddition of α,β-unsaturated benzofuran-3(2*H*)-one and azlactones (1) followed by spontaneous decarboxylation. The complete regiochemical control of tetrasubstituted pyrroles was confirmed by the orthogonal synthesis of complementary regioisomers (7a and 7b) simply by using different azlactones (1a and 1b, respectively).

Many bioactive natural products and synthetic drugs contain a pyrrole moiety as their key skeleton.[1] Pyrrole is one of the well-known heterocycles that displays remarkable biological activities such as antibacterial,[2] antiviral,[3] antitumor,[4] antioxidative,[5] and anti-inflammatory properties.[6]

In particular, tetra- and pentasubstituted pyrroles have been identified as pharmacophores for the anti-inflammatory and anticancer drug: atorvastatin (Lipitor), a top-selling drug that is used as an antihyperlipidemic agent.[7] Therefore, highly substituted pyrroles have been one of the major targets in synthetic chemistry. Many methods for the efficient synthesis of pyrrole have been reported, which can be categorized as follows: the classical Paal−Knorr synthesis,[8] the Hantzsch procedure,[9] cyclization,[10] and cycloaddition strategies.[7d,11] Although these synthetic protocols have been proven to be

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useful for the synthesis of pyrrole derivatives, the desired products are yielded as regioisomeric mixtures, particularly in the case of cycloaddition strategies, which limits the scope of synthetic modification. Further, there are only a limited number of synthetic reports on the control of the regiochemistry of pyrroles prepared via cycloaddition.[7d,11] In fact, most of the reported cycloaddition approaches have used symmetric alkynes to avoid the regioselectivity issue or have achieved only low regioselectivity when using nonsymmetric alkynes or alkenes.

To address this issue, we pursued a regioselective synthesis of tetrasubstituted pyrroles **3** via the 1,3-dipolar cycloaddition of α,β-unsaturated benzofuran-3(2*H*)-ones **2**[10c] with azlactones **1**,[11a,12] followed by spontaneous decarboxylation. To accelerate the 1,3-dipolar cycloaddition, we introduced Lewis acids and bases to activate azlactones **1**.[12d] After a systematic screening of a variety of Lewis acids [AgOAc, AgOTf, Ag_2O, $Cu(OAc)_2$, Cu_2O] and bases [2,6-lutidine, TEA, DBU], we found that though AgOAc successfully catalyzed the cycloaddition of **1** with **2**, the presence of base did not significantly influence the reaction rate. In addition, compared to the conventional thermal reaction, microwave irradiation[13] gave better results in terms of yields and reaction time. Therefore, we finalized the optimization of the standard condition as follows: microwave irradiation with 10 mol % AgOAc in anhydrous THF. As shown in Figure 1, **2** serves

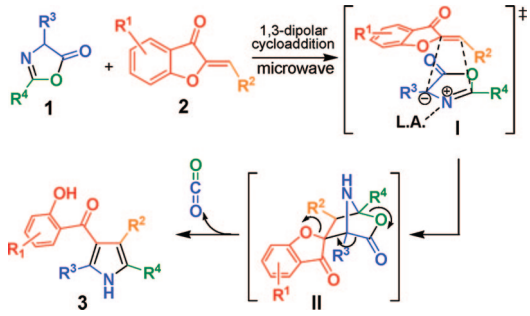
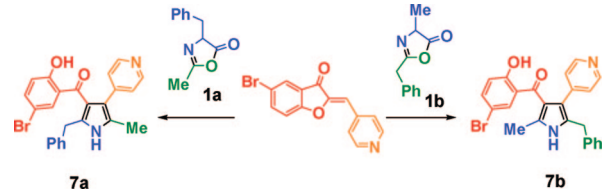


Figure 1. Potential mechanism for regioselective pyrrole synthesis via [3 + 2] cycloaddition and spontaneous decarboxylation.

as nonsymmetric dipolarophiles leading to the formation of a unique bridge-head intermediate **II** through the regioselective [3 + 2] cycloaddition with 1,3-dipole **1** (azlactones).[12c,d] The transient intermediate **II** was converted to pyrrole derivatives through spontaneous decarboxylation and subsequent ring opening of benzofuran-3(2*H*)-one, which is a key step for this transformation.

The nearly complete control of the regiochemistry in tetrasubstituted pyrroles was achieved in high to excellent yields via the unique combination of α,β-unsaturated benzofuran-3(2*H*)-one **2** with azlactones **1**. To the best of our knowledge, the generation of pyrroles through [3 + 2] cycloaddition was generally achieved using disubstituted alkynes as dipolarophiles, and the best regioselectivity was achieved in the regioisomeric ratio of 5:1.[11c] We confirmed the complete regiochemical control of tetrasubstituted pyrroles by the orthogonal synthesis of complementary regioisomers (**7a** and **7b**) simply using different azlactones (**1a** and **1b**) from *N*-acetylated phenylalanine and *N*-2-phenylacetylated alanine, respectively (Scheme 1). The two resulting

Scheme 1. Orthogonal Synthesis of Complementary Regioisomers



regioisomers were confirmed by X-ray crystallography and 1D NOE ^{1}H NMR spectroscopy (see Supporting Information). Therefore, we can incorporate four different substituents on pyrroles simply by using different building blocks and thus maximize the molecular diversity on the pyrrole core skeleton.

To gain insight into the mechanism of this transformation, various substituents at the R^1 and R^2 positions of dipolarophiles **2** were probed for their electronic effects in the 1,3-dipolar cycloaddition reaction. Upon substituting R^2 with electron-donating groups, the reaction time was found to increase from 10 to 35 min (Table 1, entries 1−4). Similarly, when R^1 was substituted with electron-donating groups and a 2-methoxyphenyl moiety was fixed at the R^2 position, the reduction of reaction rate was observed (Table 1, entries 4, 5, and 7). By using electron-withdrawing groups such as a bromo or nitro group at the R^1 position, the 1,3-dipolar cycloaddition of **2** with 2-methyl-4-phenyloxazol-5(4*H*)-one **4** exhibited excellent regioselectivity and yields (Table 1,

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Table 1. Electronic Effect of α,β-Unsaturated Benzofuranones

entry	cpd	R^1	R^2	time (min)	regioisomeric ratio[a]	yield (%)
1	**5a**	5-Br	2-nitrophenyl	10	≫99:1	90
2	**5b**	5-Br	phenyl	25	≫99:1	87
3	**5c**	5-Br	2-ethylphenyl	25	≫99:1	93
4	**5d**	5-Br	2-methoxyphenyl	35	≫99:1	94
5	**5e**	5-NO_2	2-methoxyphenyl	15	≫99:1	87
6	**5f**	5-OMe	2-bromophenyl	35	98:2	87
7	**5g**	5-OMe	2-methoxyphenyl	45	91:9	85
8	**5h**	4-OMe	2-methoxyphenyl	75	97:3	84

[a] Regioisomeric ratio was determined by LC-MS of crude product.

entries 1−5). However, when a methoxy substituent was introduced at the R^1 position, only moderate regioselectivity was obtained, even when an electron-withdrawing group was present at R^2 position (Table 1, entries 6−8). In general, we witnessed a decrease in the regioselectivity along with an extension in the reaction time. Thus, we successfully demonstrated the substrate generality of α,β-unsaturated benzofuran-3(2*H*)-ones **2** using various substituents at the R^1 and R^2 positions. We also confirmed that our novel synthetic protocol for tetrasubstituted pyrroles can offer excellent regioselectivity when the substituent at R^1 position is an electron-withdrawing group, particularly a 5-bromo group.

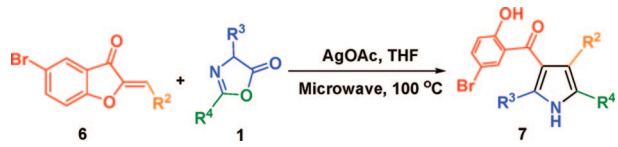
On the basis of the fact that electron-withdrawing groups on either R^1 and R^2 positions of dipolarophile **2** can significantly enhance the reaction rate, we could speculate that α,β-unsaturated benzofuran-3(2*H*)-one **2** acts as the lowest unoccupied molecular orbital (LUMO), whereas azlactone **1** acts as the highest occupied molecular orbital (HOMO) of the [3 + 2] cycloaddition. To rationalize this reaction pattern, theoretical calculation was carried out using Materials Studio 4.2 program.[14] The frontier molecular orbital (FMO) energy calculation generates HOMO and LUMO energies of **2** and **4**, either as dipole or as dipolarophile. As shown in Table 2, $\Delta E(|\text{LUMO}(\mathbf{2}) - \text{HOMO}(\mathbf{4})|)$ is systematically smaller than $\Delta E(|\text{HOMO}(\mathbf{2}) - \text{LUMO}(\mathbf{4})|)$, which is consistent with the experimental presumption, that is, that **2** serves as LUMO and **4** as HOMO.

At this point, we proceeded to validate the reaction generality using various substituents at the R^2, R^3, and R^4 positions with a fixed 5-bromo group at the R^1 position in order to ensure high regioselectivity (Table 3). The tolerance at the R^2 position was demonstrated through the introduction of various heterocyclic moieties: 4-pyridinyl (**7a**−**j**), 2-meth-

Table 2. HOMO and LUMO Energy of Individual Reaction Partners: α,β-Unsaturated Benzofuran-3(2*H*)-ones **2** and 2-Methyl-4-phenyloxazol-5(4*H*)-one **4**

2	HOMO (eV) LUMO (eV)	**4** LUMO (eV) **4** HOMO (eV)	**5**	$\Delta E(\lvert\text{HOMO}(\mathbf{2}) - \text{LUMO}(\mathbf{4})\rvert)$ $\Delta E(\lvert\text{LUMO}(\mathbf{2}) - \text{HOMO}(\mathbf{4})\rvert)$
	−5.95799	−1.78575		4.17224
2a	**−4.00029**	**−5.96607**	**5a**	**1.96578**
	−5.60133	−1.78575		3.81558
2b	**−3.40989**	**−5.96607**	**5b**	**2.55618**
	−5.51526	−1.78575		3.72951
2c	**−3.36442**	**−5.96607**	**5c**	**2.60165**
	−5.32601	−1.78575		3.54026
2d	**−3.24972**	**−5.96607**	**5d**	**2.71635**
	−5.50824	−1.78575		3.72249
2e	**−3.40798**	**−5.96607**	**5e**	**2.55809**
	−5.32013	−1.78575		3.53438
2f	**−3.28923**	**−5.96607**	**5f**	**2.67684**
	−4.89808	−1.78575		3.11233
2g	**−2.86642**	**−5.96607**	**5g**	**3.09965**
	−4.97911	−1.78575		3.19337
2h	−2.70919	−5.96607	**5h**	3.25688

Table 3. Diversity of Pyrrole Synthesis via [3 + 2] Cycloaddition



compd	R^2 (aldehyde)	R^3 (amino acid)		R^4 (acyl)	yield[a] (%)
7a	4-pyridinyl	benzyl	(Phe)	methyl	90
7b	4-pyridinyl	methyl	(Ala)	benzyl	75
7c	4-pyridinyl	phenyl	(Phg)	methyl	93
7d	4-pyridinyl	isobutyl	(Leu)	methyl	79
7e	4-pyridinyl	2-(methylthio)ethyl	(Met)	methyl	70
7f	4-pyridinyl	(1*H*-imidazol-5-yl)methyl	(His)	methyl	86
7g	4-pyridinyl	phenyl	(Phg)	cyclohexyl	97
7h	4-pyridinyl	phenyl	(Phg)	phenyl	94
7i	4-pyridinyl	phenyl	(Phg)	benzyl	91
7j	4-pyridinyl	phenyl	(Phg)	*n*-butyl	95
7k	2-methoxyphenyl	methyl	(Ala)	methyl	91
7l	4-methoxyphenyl	phenyl	(Phg)	methyl	97
7m	3-nitrophenyl	phenyl	(Phg)	methyl	91
7n	2-thiophenyl	phenyl	(Phg)	methyl	84

[a] Yield was obtained on the basis of the recovered starting materials **6**.

oxyphenyl (**7k**), 4-methoxyphenyl (**7l**), 3-nitrophenyl (**7m**), and 2-thiophenyl group (**7n**). In addition, the scope of the substituents at the R^3 positions of azlactones **1** was systematically expanded by using natural or unnatural amino acids (Phe, Ala, Leu, Met, His, and Phg). In case of Met and His, the desired pyrroles **7e** and **7f** were prepared in moderate to good yields even with the presence of unprotected internal nucleophiles. Finally, the introduction of various substituents at the R^4 position was pursued by using different acylating agents (acetyl, benzoyl, 2-phenylacetyl, pentanoyl, and *cyclo*-hexanecarbonyl). In all the cases of this study, substitutents at the R^4 position did not influence the regioselectivity and reaction rate except in the case of benzoylation, which demonstrated the slightly reduced regioselectivity (see Supporting Information).

In conclusion, we developed a novel regioselective synthesis of tetrasubstituted pyrroles via the classic 1,3-dipolar cycloaddition of α,*β*-unsaturated benzofuran-3(2*H*)-one **2** and azlactones **1** followed by spontaneous decarboxylation. In particular, we could achieve excellent regioselectivity when **2** was substituted with electron-withdrawing groups. Thus, molecular diversity on biologically useful tetrasubstituted pyrroles can be introduced by simply changing easily accessible moieties, i.e., hydroxyacetophenones (R^1), aldehydes (R^2), amino acids (R^3), and acylating agents (R^4); further, we could achieve high regioselectivity and good to excellent yields. Further modification and diversification as well as the associated biological evaluation of these tetrasubstituted pyrroles will be reported in due course.

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Supporting Information Available: Experimental details, X-ray structure, and copies of ^1H and ^{13}C NMR spectra of all compounds **5a**−**7n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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