Letter

Copper-catalyzed [4+2]-Cycloadditions of Isoxazoles with 2-Alkynyl Benzaldehydes to Access Distinct #-Carbonylnaphthalene Derivatives: C(3,4)- versus C(4,5)-Regioselectivity at Isoxazoles

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Copper-catalyzed [4+2]-Cycloadditions of Isoxazoles with 2-Alkynyl Benzaldehydes to Access Distinct α-Carbonylnaphthalene Derivatives: C(3,4)- versus C(4,5)-Regioselectivity at Isoxazoles

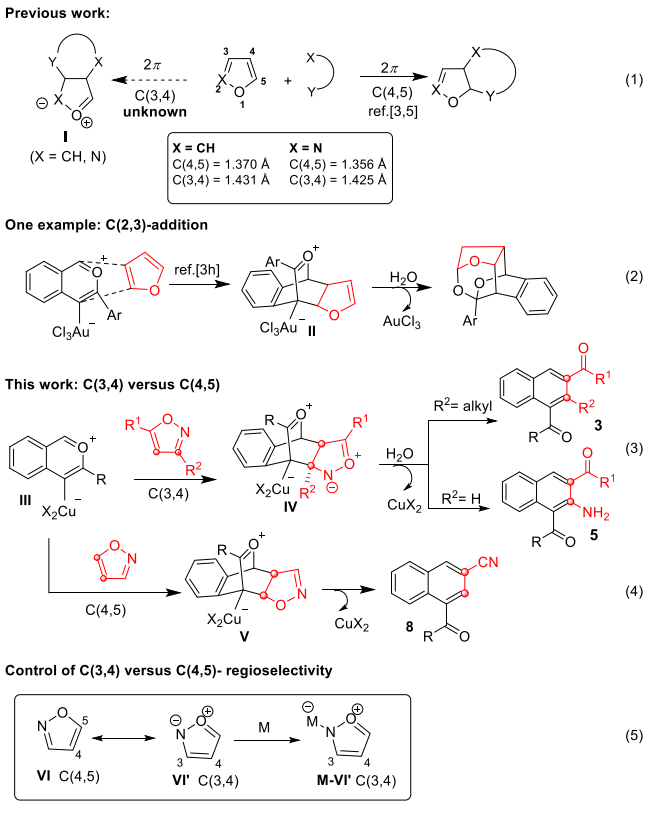
Sovan Sundar Giri and Rai-Shung Liu*

Frontier Research Centre on Fundamental and Applied Sciences of Matters, Department of Chemistry, National Tsing-Hua University, No. 101, Section 2, Kuang-Fu Road, Hsinchu, Taiwan 30013, R.O.C.

KEYWORDS. Cycloaddition, benzopyrylium, isoxazole, C(3,4)-carbons, 2π-donor.

ABSTRACT: Cu(II)-catalyzed [4+2]-cycloadditions occur between Cu-benzopyryliums and substituted isoxazoles with the regioselectivity on the C(3,4)-carbons of isoxazoles. We postulate that a prior coordination of isoxazoles with $Cu(OAc)_2$ increases the π-bond character of the C(3,4) carbons to become an effective 2π donor. In this reaction sequence, 3,5-disubstituted isoxazoles yield α,γ-dicarbonylnaphthalenes whereas, 5-substituted isoxazoles deliver α,γ-dicarbonyl-β-aminonaphthalenes. For unsubstituted isoxazole, its cycloaddition chemoselectivity is switched to the C(4,5)-addition regioselectivity to yield α-carbonyl-γ-cyanonaphthalene derivatives.

Metal-catalyzed cycloadditions emerge as powerful tools to construct complicated carbocyclic and heterocyclic frameworks.[1] Aromatic heterocycles such as furans are well documented to serve as 4π-[2] or 2π-donors[3] to undergo catalytic cycloadditions with π-bond motifs or 1,n-dipoles. Apart from furans, isoxazoles are appealing 4π- or 2π-donors in catalytic cycloadditions,[4,5] which are accessible to valuable nitroxy (*N-O*)-containing heterocycles.[6] In the context of 2π-systems, the C(4,5)-carbons of furans and isoxazoles are the exclusive sites for the cycloadditions without no exception (eq 1).[3,5a-d] The large C(3,4) distances[7] in furan (1.431 Å) and isoxazole (1.425 Å) show small π-bond character that renders difficult their C(3,4)-cycloadditions. Eq 2 shows one example between a [4+2]-cycloaddition of furan and gold-containing benzopyrylium, in which the furanyl C(2,3) carbons are the reaction sites.[3h] Herein, we sought to develop novel cycloadditions at the C(3,4)-carbons of furans or isoxazoles, generating carbonyl ylide intermediates (**I**, eq 1).[8] In chemical reactivity, we envisage that isoxazoles are typically represented by the structure (**VI**, eq 5) whereas the other resonance form **VI'** is generally less significant. This reactivity pattern can be altered when isoxazole is complexes with an electrophilic catalyst to form **M-VI'**. To realize this hypothesis, this work discloses Cu-catalyzed [4+2]-cycloadditions of substituted isoxazoles with benzopyryliums (**III**),[9] in which the C(3,4) carbons of isoxazoles are activated by Cu(II) to serve effectively as 2π-donors, further delivering α,γ-dicarbonylnaphthalenes **3** and α,γ-dicarbonyl-β-aminonaphthalenes **5** respectively (eq 3). In the case of unsubstituted isoxazole, the chemoselectivity is switched to C(4,5)-carbons to deliver α-carbonyl-γ-cyanonaphthalene products **8** (eq 4). Importantly, this catalytic system is accessible to three distinct



naphthalene derivatives bearing useful amine, cyano and carbonyl functionalities, further manifesting the synthetic utility.

The importance of this new catalysis is the one-pot synthesis of 2-carbonyl-3-aminonaphthalene derivatives **5** that are structural cores for several bioactive molecules

(Figure 1, **I-IV**).[10] Rifampicin is used as an antitubercular agent[10a] while PI-083(NSC45382)[10b] and (-)-*N*-methylguattescidine[10c] serve as anticancer agents. Compound **IV** is in phase-1 clinical trial under code name S23906-1 for its potent cytotoxic effects.[10d] Notably, chemical derivations of compounds **5** afford new polyaromatic molecules that have the same structural cores as several bioactive molecules (*vide infra*).

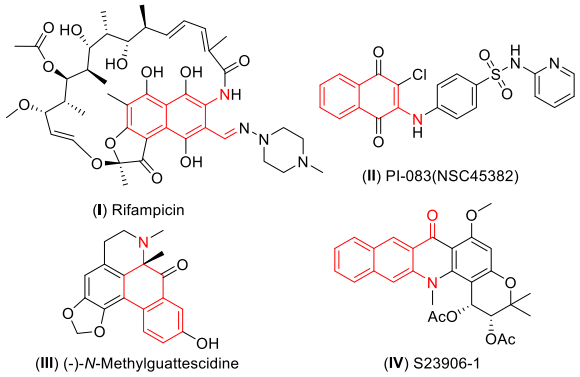
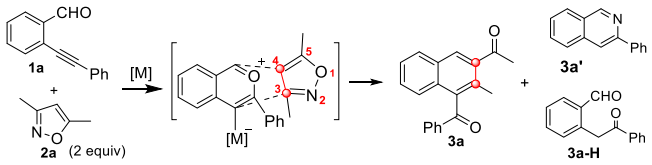


Figure 1. Representative bioactive molecules.

Table 1 summarizes the optimized conditions for catalytic cycloadditions of 2-(phenylethynyl)benzaldehyde **1a** with 3,5-dimethylisoxazole **2a** and with varied copper catalysts. Heating this mixture (**1a**/**2a** = 1:2) in hot

Table 1. [4+2]-Cycloadditions Over Various Copper salts



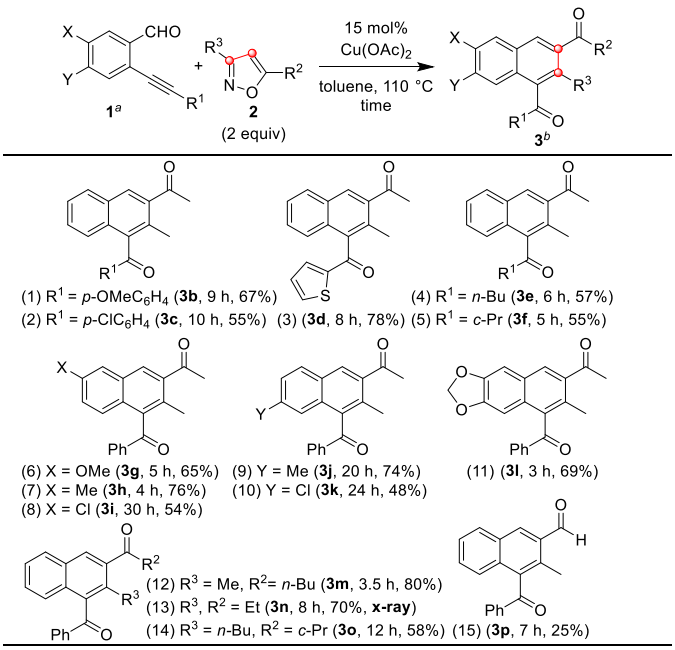
entry	catalyst (mol%)[a]	solvent	*T*[°C] /*t*[h]	yield[b] (%)			
				1a	**3a-H**	**3a'**	**3a**
1	$CuCl_2$(10)	toluene	110/ 24	20	--	13	55
2	$Cu(OTf)_2$(10)	toluene	110/ 20	--	--	--	21
3	$Cu(acac)_2$(10)	toluene	110/ 24	38	8	--	14
4	CuI(10)	toluene	110/ 24	96	--	--	--
5	$Cu(OAc)_2$(10)	toluene	110/ 16	--	--	14	63
6	$Cu(OAc)_2$(10)	PhCl	120/ 16	--	15	7	46
7	$Cu(OAc)_2$(10)	DCE	80/ 24	55	20	--	12
8	$Cu(OAc)_2$(10)	ACN	80/ 24	52	27	--	8
9	$Cu(OAc)_2$(10)	THF	70/ 24	95	--	--	--
10	**$Cu(OAc)_2$(15)**	**toluene**	**110/ 7**	--	**8**	**9**	**72**
11	IPrAuCl/ $AgNTf_2$(10)	DCE	80/15	--	9	--	--
12	$Zn(OTf)_2$(20)	DCE	80/20	66	13	--	--
13	$PtCl_2$(10)	DCE	80/15	36	15	--	--

[a] **1a** = 0.3 M. [b] Product yields are reported after separation from silica column. DCE = 1,2-dichloroethane; ACN = acetonitrile; IPr = 1,3-bis(diisopropylphenyl)-imidazol-2-ylidene.

toluene (110 °C) with $CuCl_2$ (10 mol %) afforded 1-(4-benzoyl-3-methylnaphthalen-2-yl) ethan-1-one **3a** in 55% yield (entry 1). A switch to $Cu(OTf)_2$ and $Cu(acac)_2$ delivered desired **3a** in only 14-21% yields. For acidic Cu(OTf)2 one byproducts **3a"** was obtained in 30% yield (see Scheme s1, SI) whereas less acidic $Cu(acac)_2$ gave unreacted **1a** and an alkyne hydration **3a-H** in 38% and 8% yields respectively. CuI was entirely catalytically inactive (entries 2-4). With $Cu(OAc)_2$ (10 mol %) in toluene and chlorobenzene, the yields of the desired product **3a** were 63% and 46% respectively (entry 5-6). Other solvents such as DCE, acetonitrile and THF were inappropriate for this new reaction (entries 7-9). With a 15 mol % loading of $Cu(OAc)_2$, our target **3a** was isolated in 72% yield (entry 10). We also tested other catalysts such as IPrAuCl/$AgNTf_2$, $Zn(OTf)_2$ and $PtCl_2$, each at 10-20 mol % loading, but our target **3a** was not produced at all (entries 11-13). In the case of gold catalyst, one hydrative dimerization of compound **1a** occurred to give **3b"**/**3c"** was isolated in 15% and 20% as depicted in SI (Scheme s1). The molecular structure of compound **3a** was inferred from its relative **3n**[11] and the ^{1}H NOE spectra matched well with this proposed structure.

We assessed the generality of these new reactions between 2-alkynyl benzaldehydes **1** and 3,5-disubstituted isoxazoles **2**; the results are summarized in Table 2. For 2-alkynyl benzaldehydes **1b-1c** bearing various 4-phenylalkynyl groups (R^1 = 4-XC_6H_4, X = OMe and Cl), their reactions with 3,5-dimethyl isoxazole **2a** afforded

Table 2. Catalytic Synthesis of *α,γ*-Dicarbonyl Naphthalenes



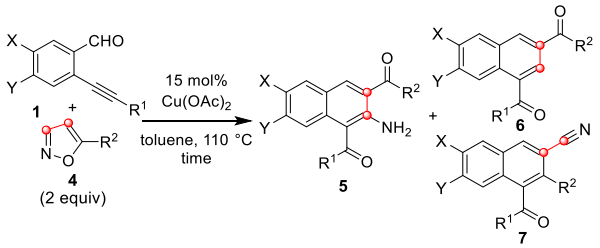
[a] **1** = 0.3 M. [b] Product yields are reported after separation from silica column.

desired **3b-3c** in 67% and 55% yields respectively (entries 1-2, Table 2). 2-Thienylalkynyl derivative **1d** was also an applicable substrate to yield compound **3d** in 78% yield (entry 3). Alkylalkynyl derivatives **1e** and **1f** (R^1 = *n*-butyl and cyclopropyl) reacted well with 3,5-dimethylisoxazole **2a** to deliver the corresponding products **3e-3f** in 55-57% yields (entries 4-5). For 2-alkynyl benzaldehydes **1g-1i** bearing 4-phenyl substituents (X = OMe, Me and Cl),

their resulting products **3g-3i** were obtained in 54-76% yields (entries 6-8). We also tested the reactions on 5-phenyl derivatives **1j** and **1k** (Y = Me and Cl), affording expected products **3j-3k** in moderate yields (48-74%, entries 9-10). In the case of benzodioxole-derived species **1l**, its reaction with 3,5-dimethylisoxazole **2a** gave compound **3l** in 69% yield (entry 11). We varied the 3,5-disubstituents of isoxazoles **2b**, **2c** and **2d** with large alkyl groups, (R^3, R^2 = Me, *n*-Bu; Et, Et and *n*-Bu, cyclopropyl); their corresponding products **3m-3o** were obtained in 58-80% yields (entries 12-14). The molecular structure of compound **3n** was characterized with X-ray diffraction.[11] For 3-methylisoxazole **2e**, its Cu-catalyzed reaction with aldehyde **1a** afforded compound **3p** in 25% yield (entry 15); this small yield indicates the importance of a C(5)-alkyl substituent (R^2) to stabilize a carbonyl ylide **I** in eq 1. Notably, 5-phenyllisoxazole was inapplicable substrate because the phenyl is an electron-withdrawing group.

The lack of a C(3)-substituent of isoxazoles greatly affects the reaction chemoselectivity. As shown in Table 3, we performed Cu-catalyzed reactions with 5-substituted isoxazoles **4**; notably, the chemoselectivity was altered to deliver distinct *β*-amino *α,γ*-dicarbonyl naphthalene compounds **5** (Table 3). The Cu-catalyzed reaction of 2-(phenylethynyl)benzaldehyde **1a** with 5- methylisoxazole **4a** afforded compound **5a** in 76% yield whereas its tolylalkynyl analogue **1m** gave similar compound **5b** in 71% yield (entries 1-2).

Table 3. Catalytic Synthesis of *β*-Amino *α,γ*-Dicarbonyl Naphthalenes

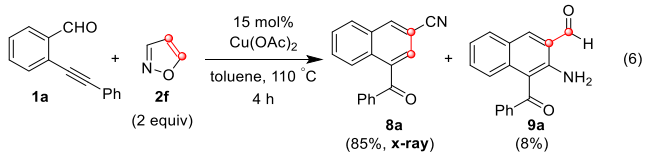


(1) R^1 = Ph (**5a**, 5 h, 76%)[a,b]
(2) R^1 = *p*-tolyl (**5b**, 4 h, 71%), (**6b**, 5%), (**7b**, 15%)
(3) R^1 = *n*-Bu (**5c**, 3 h, 68%), (**6c**, 8%)
(4) R^1 = *c*-Pr (**5d**, 2 h, 36%), (**7d**, 4%)
(5) X = OMe (**5e**, 5 h, 69%), (**7e**, 18%)
(6) X = Cl (**5f**, 7 h, 51%), (**6f**, 13%), (**7f**, 18%)
(7) Y = Me (**5g**, 12 h, 81%), (**7g**, 16%)
(8) Y = Cl (**5h**, 2.5 h, 48%), (**6h**, 4%)
(9) R^2 = styryl (**5i**, 0.7 h, 32%), (**6i**, 7%)
(10) R^2 = *n*-Bu (**5j**, 6 h, 48%), (**6j**, 26%)
(11) R^2 = Bn (**5k**, 6 h, 51%, **x-ray**), (**6k**, 25%)

[a] **1** = 0.3 M. [b] Product yields are reported after separation from a silica column.

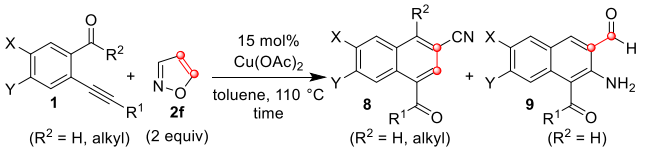
Alkylalkynyl derivatives **1e-1f** (R^1 = *n*-butyl and cyclopropyl) afforded desired **5c-5d** in reasonable yields (36-68%, entries 3-4). Similarly, the presence of 4-substituents at the bridging benzene (X = OMe, Cl; Y = H) in substrates **1g** and **1i** were compatible with the reactions to afford the desired products **5e-5f** in 69% and 51% yields (entries 5-6). 5-Phenyl substrates **1j** and **1k** (Y = Me and Cl) were also catalytically active to produce compounds **5g** and **5h** in 81% and 48% yields (entries 7-8). We tested the reactions on various 5-substituted isoxazoles **4b-4d** (R^2 = styryl, *n*-butyl and benzyl), producing compounds **5i-5k** in moderate yields (32-51%, entries 9-11). The molecular structure of compound **5k** was characterized by X-ray diffraction.[11]

The reaction chemoselectivity is completely altered when unsubstituted isoxazole **2f** is used to react with model molecule **1a** to afford compounds **8a** and **9a** in 85% and 8% yields respectively (eq 6); the former arises from a



typical C(4,5)-cycloaddition whereas the latter follows a novel C(3,4)-cycloaddition. The molecular structure of compound **8a** was confirmed with X-ray diffraction.[11] Accordingly, the C(3,4)-cycloaddition of isoxazoles relies on the presence of an alkyl group, especially on the C(5)-carbon to stabilize a carbonyl ylide **I** (eq 1).

Table 4. Cu-Catalyzed Synthesis of *α*-Carbonyl-*γ*-cyanonaphthalenes



(1) R^1 = *p*-$OMeC_6H_4$ (**8b**, 6 h, 72%),[a,b] (**9b**, 18%)
(2) R^1 = *p*-ClC_6H_4 (**8c**, 3.5 h, 85%), (**9c**, 8%)
(3) (**8d**, 2 h, 80%), (**9d**, 17%)
(4) R^1 = *n*-Bu (**8e**, 5 h, 75%), (**9e**, 15%)
(5) R^1 = *c*-Pr (**8f**, 3 h, 48%), (**9f**, 33%)
(6) (**8g**, 4 h, 68%), (**9g**, 28%)
(7) X = OMe (**8h**, 5 h, 87%), (**9h**, 7%)
(8) X = Me (**8i**, 4 h, 65%), (**9i**, 12%)
(9) X = Cl (**8j**, 2 h, 80%), (**9j**, 5%)
(10) (**8k**, 3 h, 78%, **x-ray**)

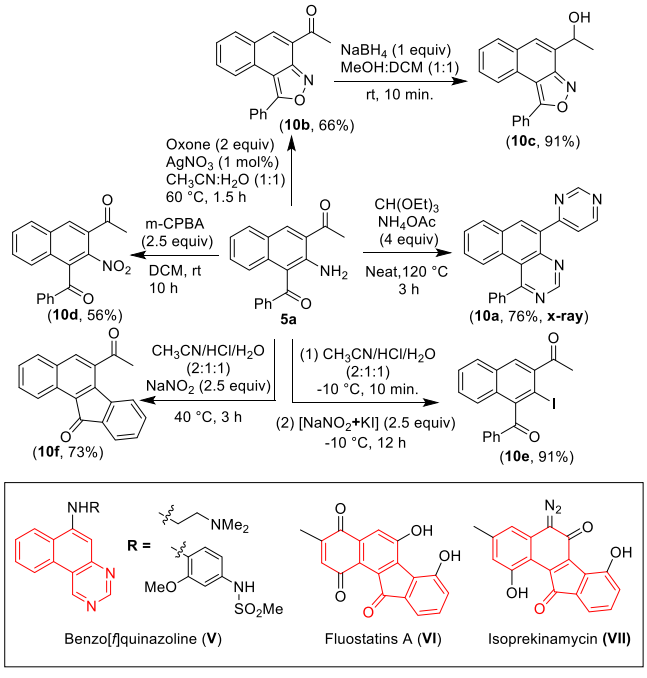
[a] **1** = 0.3 M. [b] Product yields are reported after separation from a silica column.

The value of this copper-catalyzed reaction is to provide distinct naphthalene compounds **8** that are difficult to prepare from other methods. For all cases, additional by-products **9**, resulting from the C(3,4)-addition in Table 4,

were obtained in minor proportions. We tested the reactions of isoxazole **2f** with 2-alkynylbenzaldehydes **1b-1d** bearing various arylalkynes (R^1 = *p*-$OMeC_6H_4$, *p*-ClC_6H_4 and 2-thienyl), affording the desired compounds **8b-8d** in satisfactory yields (72-85%, entries 1-3). For alkylalkynyl derivatives **1e-1f** (R^1 = *n*-butyl and cyclopropyl), their resulting products **8e** and **8f** were in 75% and 48% yields respectively (entries 4-5). For benzodioxole-derived species **1l** and 4-substituted phenyl benzaldehydes **1g-1i** (X = OMe, Me and Cl), their resulting cycloaddition products **8g-8j** were obtained in 65-87% yields (entries 6-9). We also prepared 2-(phenylethynyl)acetophenone **1n** that afforded the desired product **8k** in 78% yield (entry 10). The molecular structure of compound **8k** was confirmed with x-ray diffraction.[11]

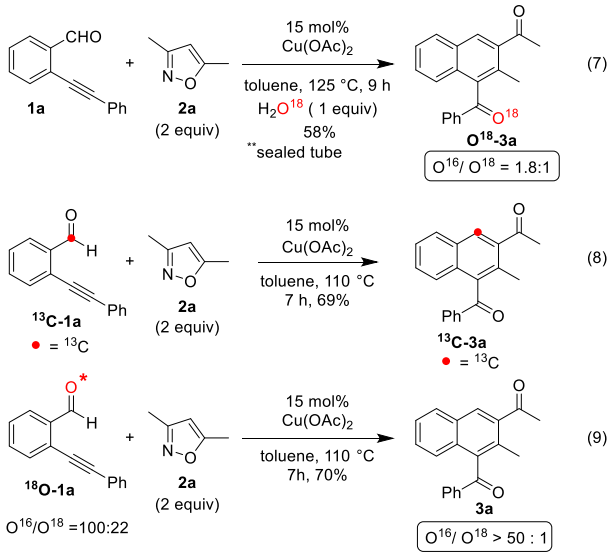
The amine and two ketones of compound **5a** enable various chemical functionalizations. Treatment of this compound with neat $CH(OEt)_3$ and $NH_4(OAc)$[12] produced 1-phenyl-5-(pyrimidin-4-yl)benzo[*f*]quinazoline **10a** in 76% yield. The molecular structure of compound **10a** was characterized with X-ray diffraction.[11] The oxidation of compound **5a** with oxone[13] gave 1-phenylnaphtho[2,1-*c*]isoxazol **10b** in 66% yield whereas the *m*-CPBA oxidation delivered *β*-nitro-*α,γ*-dicarbonyl naphthalene **10d** in 56% yields respectively. $NaBH_4$-reduction of species **10b** produced an ethan-1-ol derivative **10c** in 91% yield. Employing a Sandmeyer reaction[14] at -10 °C, compound **5a** was convertible to *β*-iodo-*α,γ*-dicarbonyl naphthalene **10e** in 91% yield. Finally, diazotization of **5a** induced an intramolecular cyclization to give 6-acetyl-11*H*-benzo[*a*]fluoren-11-one **10f** in 73% yield.

Scheme 1. Functionalization of One Representative Compound 5a



The value of these derivation reactions provides highly matchable cores of selected bioactive molecules such as benzo[*f*]quinazolines (**V**),[15a] fluostatins A(**VI**) and isoprekinamycin (**VII**)[15b]. Benzo[*f*]quinazolines derivatives have shown antiproliferative effect on human tumor cell lines, whereas, fluostatins A is a selective inhibitor of the enzyme dipeptidyl peptidase III. Isoprekinamycin is a metabolite isolated from *Streptomyces murayaensis*.

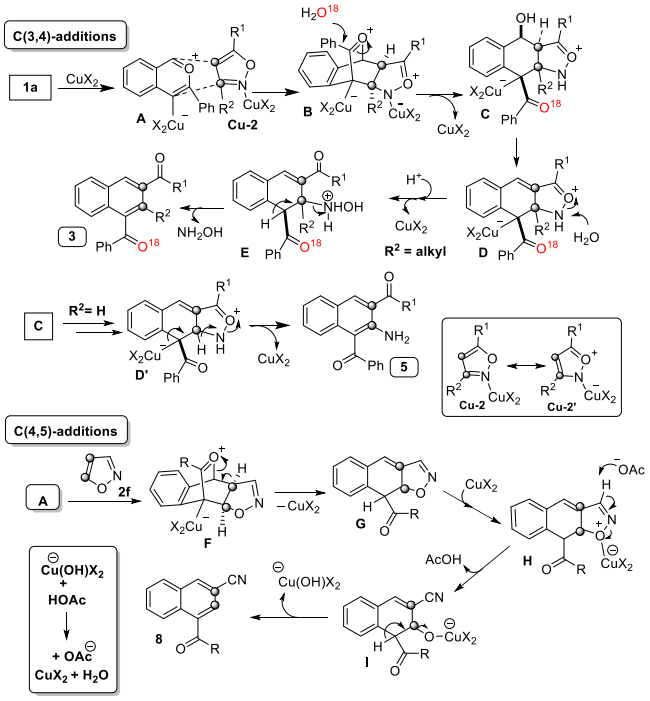
We conducted an O^{18} labeling experiment on a mixture of reactants **1a** and **2a**, yielding compound **O^{18}-3a** bearing only one O^{18} atom in ratio O^{16}/O^{18} = 1.8:1 (eq 7). A loss of ^{18}O content is due to the presence of residual water in this system. From an analysis of the EI-MS fragmentation (see SI), two fragments, 245.0962 (O^{16}) and 247.1009 (O^{18}), in intensity ratio 2.1:1, were detected and assigned to be [M–MeCO]$^+$. These two fragments indicate that the ^{18}O-atom was labeled on the phenylketone oxygen of species **O^{18}-3a**. For initial **^{13}C-1a** bearing 10 % ^{13}c-content at the aldehyde, it resulting product **^{13}C-3a** comprised ^{13}C-content only at the C(4)-carbon, indicating no carbonyl migration (eq 8). We also tested the reaction on **^{18}O-1a** bearing 25% ^{18}O content at its aldehyde, but its corresponding product **3a** contained no ^{18}O-oxygen (eq 9).



Structural analysis of major products **3** or **5** indicates that the C(3,4)-cycloadditions of isoxazoles **2** are viable routes. A plausible mechanism is provided in Scheme 2. Only unsubstituted isoxazole **2f** (R^1 = R^2 = H) undergoes a typical C(4,5)-cycloaddition (eq 6). We postulate that $Cu(OAc)_2$ first reacts with an isoxazole to form a complex pair **Cu-2**, in which the C(3,4) bond has significant *π*-bond character, as shown the resonance structure **Cu-2'**. An initial [4+2]-cycloaddition[9] between Cu-containing benzopyrylium **A** and species **Cu-2** generates species **B**, of which the oxonium group is attacked by water according to an ^{18}O-labeling experiment (eqs 7 and 9). This hydrolysis reaction is expected to yield species **C** that undergoes dehydration to give unsaturated oxonium species **D**. We postulate that the positive charge of species **E** locates mainly at the benzylic carbon so that cleavage of the *N-O* bond is initiated by an attack of water at the amino *N-H* moiety, yielding species **E** for those isoxazoles **2** bearing R^2 = alkyl. An elimination of NH_2OH from species **E** is expected to form products **3**. For C(5)-substituted isoxa-

zole **4** (R^2 = H), the corresponding C(3,4)-isoxazole cycloaddition affords intermediate **D'** that can induce cleavage of a *N-O* bond to produce the observed products **5** through a loss of $Cu(OAc)_2$ and a proton transfer. The proposed complex pair **Cu-2** also rationalizes the distinct behavior of unsubstituted isoxazole **2f** (eq 6), for which formation of a complex with $Cu(OAc)_2$ is difficult because an alkyl group to enhance the nitrogen basicity is lacking.

Scheme 2. A Plausible Reaction Mechanism



Formation of *α*-ketonyl-*γ*-cyanonaphthalene **8** from unsubstituted isoxazole **2f** arises from the C(4,5)-cycloadditions. Following a similar path, an initial [4+2]-cycloaddition between Cu-benzopyrylium **A** and isoxazole generates species **G** that subsequently undergoes a Cu-assisted deprotonation through intermediate **H**, yielding species **I** and ultimately the observed product through an aromatization.

In summary, this work reports the first success for Cu-catalyzed [4+2]-cycloadditions[16] of benzopyryliums with substituted isoxazoles, in which the regioselectivity of isoxazoles occurs on the C(3,4)-carbons. This chemoselectivity is astonishing because the C(3,4) bond of isoxazoles has little *π*-bond character. We postulate that a prior bonding of isoxazoles with $Cu(OAc)_2$ activates the C(3,4) bond *via* an increased *π*-bond character. In this reaction sequence, 2,5-disubstituted isoxazoles afford *α,γ*-dicarbonylnaphthalenes whereas 5-substituted isoxazoles afford *α,γ*-dicarbonyl-*β*-aminonaphthalenes. In the case of unsubstituted isoxazole, a typical C(4,5)-addition regioselectivity is observed with formation of *α*-ketonyl-*γ*-cyanonaphthalenes. The use of one 2-alkynyl benzaldehyde to access three distinct classes of highly functionalized naphthalene products highlights the synthetic utility.

ASSOCIATED CONTENT

Experimental procedures, characterization data, crystallography data, and ^{1}H NMR and ^{13}C NMR for representative compounds (PDF).
This material is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

Prof. Rai-Shung Liu
*E-mail: rsliu@mx.nthu.edu.tw

ORCID

Rai-Shung Liu: 0000-0002-2011-8124

Notes

The authors declare no conflict of interest.

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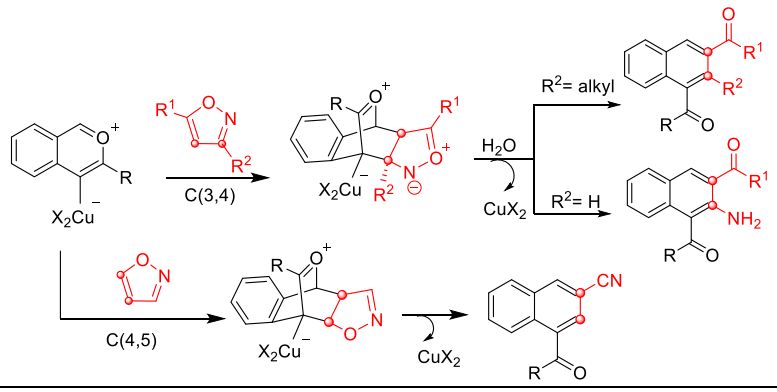
R
X2Cu
R1
R2
C(3,4)
X2Cu
H2O
CuX2
R2= alkyl
R2= H
NH2
C(4,5)
X2Cu
CuX2
CN