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Isocyano Enones: Addition–Cyclization Cascade to Oxazoles

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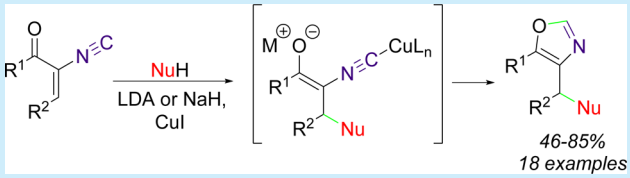
Supporting Information

ABSTRACT: Copper iodide catalyzes the conjugate addition of organometallic and heteroatom nucleophiles to isocyano enones to afford oxazoles. A range of enolates, metalated nitriles, amines, and thiols undergo catalyzed conjugate addition to cyclic and acyclic oxoalkene isocyanides. Mechanistic studies suggest that copper complexation facilitates the nucleophilic attack on the isocyano enone to generate an enolate that cyclizes onto the isocyanide leading to a variety of substituted acyclic or ring-fused oxazoles.



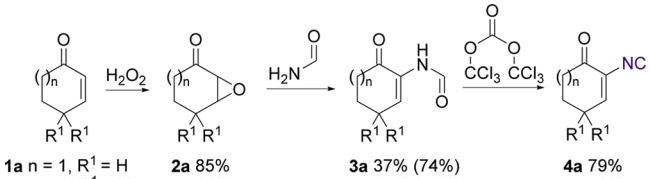
Isocyanides are exceptionally versatile precursors with unique chemical reactivity[1] and biological activity.[2] The formal divalent character of isocyanides[3] permits an array of reactivity not commonly observed with other functionality; isocyanides react with electrophiles, nucleophiles, radicals, and transition metals.[1,4] In many cases, the resulting intermediates have been harnessed in multicomponent reaction sequences where the isocyanide serves as a central connection point.[5]

Conspicuously lacking among the reactions of isocyanides are bond constructions at sites *other* than the isocyanide carbon.[1] Isocyano enones appeared to be attractive candidates to address this void because they incorporate orthogonal ketone, olefin, and isocyanide functionalities primed for sequential reactions. Activation of the olefin by both ketone and isocyanide groups was anticipated to promote conjugate addition reactions,[6] a fundamental bond construction that is largely unexplored for isocyanoalkenes.[7] Primary amines and H_2S are among the few nucleophiles that react with isocyanoalkenes, first by conjugate addition and then by reaction with the isocyanide.[8] Described below is a copper-catalyzed addition of carbon and heteroatom nucleophiles to isocyano enones that generates a diverse array of oxazoles.

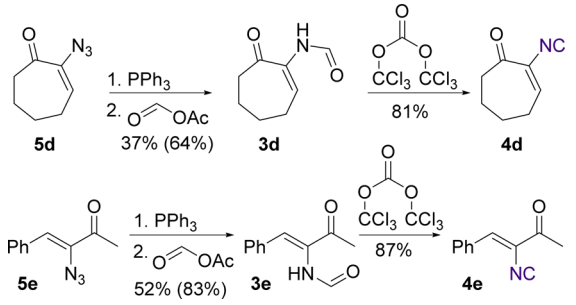
The synthesis of oxoalkene isocyanides is challenging.[9] Scouting experiments identified a short route to cyclic 5- and 6-membered isocyano enones predicated on a formamide ring-opening dehydration of epoxy ketones (Scheme 1). In practice, microwave irradiation (100 °C, 1–2 h) of 5- and 6-membered epoxyketones **2**, generated from the corresponding enones **1**,[10] provided a direct method for promoting the ring opening and dehydration to the corresponding ene formamides **3**.[11] Subsequent dehydration of the formamide functionality afforded the corresponding isocyanides **4**.[12]

Although the ring opening–dehydration route rapidly provided 5- and 6-membered isocyano enones **4a**–**4c**, the strategy was not amenable to the synthesis of 7-membered or acyclic isocyanides.[13] Consquently, a complementary sequence was developed to both cyclic and acyclic isocyano enones (Scheme 2). The strategy builds on the chemistry of vinyl azides[14] that are readily accessed from the corresponding enones by sequential bromination and treatment with azide.[15] Conversion of the vinyl azides **5d** and **5e** to the corresponding isocyanides was achieved by treatment with PPh_3 to generate an azophosphorane that was intercepted with acetic formic anhydride to afford the ene formamides **3d**

Scheme 1. Isocyano Enone Synthesis



Scheme 2. Alternate Isocyano Enone Synthesis



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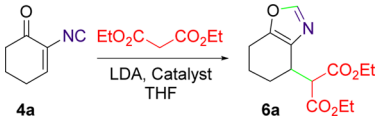
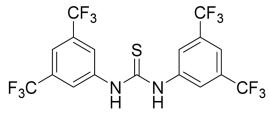
and **3e**.[11,16] Subsequent dehydration provided the isocyano enones **4d** and **4e** (Scheme 2).[17]

Isocyano enones **4** were anticipated to be particularly reactive toward nucleophilic conjugate addition because the corresponding oxoalkene nitriles are excellent Michael acceptors.[6] Attempted conjugate additions to **4a** with a variety of organometallics (RLi, RMgX, R_3MgLi, RZnX, R_2Zn, R_3ZnLi) produced complex mixtures,[18] whereas the enolate derived from diethyl malonate afforded oxazole **6a** in 10% yield (Table 1, entry 1). Screening potential catalysts identified several copper complexes as competent catalysts (Table 1, entries 7–11).[4] Further optimization of solvent (CH_2Cl_2, H_2O, DMSO, DMF, Et_2O, and THF) and base (NaH, LDA, K_2CO_3, *i*-Pr_2NEt, and KHMDS) led to an optimized procedure with catalytic CuI and either LDA or NaH in THF (Table 1, entry 11).[19]

Table 1. Malonate Conjugate Addition to 4a[a]



4a 6a

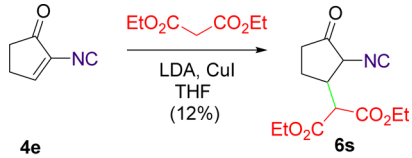
entry	catalyst	yield (%)
1	None	10
2		0[b]
3	Cu_2O	2
4	$Pd_2(dba)_3$	3
5	$Pd(PPh_3)_4$	35
6	$AgBF_4$	47
7	$CuCl_2$	51
8	CuCl	52
9	Cu(3-methyl Salicylate)	54
10	CuBr	59
11	CuI	82

[a]Reaction conditions: **4a** (0.18 mmol), diethyl malonate (0.18 mmol), LDA (0.18 mmol) catalyst (3 mol %), THF (5.0 mL), 1 h, 0 °C. [b]Performed in the absence of LDA.

The reaction scope was explored through the addition of diverse carbon and heteroatom nucleophiles to a series of isocyano enones **4** (Table 2).[20] Dicarbonyl nucleophiles such as metalated malonates, ethyl acetoacetate, and 2,4-pentanedione smoothly reacted with **4a** (Table 2, entries 1–4). Addition of diethyl 2-methylmalonate afforded **6b** with contiguous tertiary–quaternary centers (entry 2). Conjugate additions with 2-coumaranone and nitromethane (Table 2, entries 5 and 6) efficiently afforded substituted oxazoles; with malonitrile, the use of NaH proved to be more efficient than LDA (Table 2, entry 7).[21] The heteroatom nucleophiles benzylamine and 4-methylbenzenethiol readily form the corresponding oxazoles (entries 8 and 9) with *p*-TolSH undergoing conjugate addition even in the absence of base.

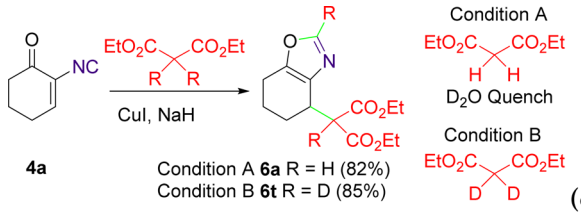
Conjugate addition of a representative suite of nucleophiles to the *gem*-dimethyl-substituted isocyanide **4b** afforded the corresponding oxazoles **6j–n** (Table 1, entries 10–14). The reactions with **4b** were less efficient and required longer reaction times (Table 2, note f) than for the *des*-methyl isocyanide **4a**[22] presumably because of the greater steric compression during C–C bond formation. Conjugate additions of diethyl malonate and malononitrile to the 7-membered and acyclic isocyano enones **4c** and **4d**, respectively, afforded the corresponding oxazoles **6o–r** (Table 1, entries 15, 16 and 17, 18, respectively). Rapid access to the fused 7-membered oxazoles **6o** and **6p** is particularly significant given the bioactivity of several structurally related marine-derived oxazolones.[23]

Efforts to extend the oxazole reaction to the 5-membered isocyano enone **4e** were not successful but provided insight into the reaction mechanism (eq 1). Exposure of **4e** to the standard conditions with diethyl malonate afforded a low yield of the isocyano enone **6s** rather than the expected oxazole. Presumably, the intermediate enolate generated from the malonate addition is unable to attack the isocyanide because of the larger bond angles enforced by the 5-membered ring.



4e 6s **(eq 1)**

Further mechanistic insight was gained from deuterium-labeling experiments. Addition of D_2O at the end of the reaction did not result in deuterium incorporation (eq 2, conditions A), suggesting that oxazole protonation occurred during the catalytic cycle.[24] The proton source was identified through the reaction of **4a** with λ-D_2-diethyl malonate, which afforded the deuterated oxazole **6t** (eq 2, condition B, 96% deuteration in the oxazole).[25]



4a

Condition A **6a** R = H (82%)
Condition B **6t** R = D (85%)

(eq 2)

Collectively, the deuteration and addition experiments suggest a catalytic cycle featuring a conjugate addition–enolate cyclization (Scheme 3). The propensity of copper(I) to complex isocyanides suggests that the active catalyst may be ligated to multiple isocyanides. Complexation of the active catalyst **8** with the oxonitrile likely facilitates the conjugate addition of the nucleophile via **9** leading to the oxazole enolate **7**. Cyclization of the alkoxide onto the copper-complexed isocyanide (**7** → **10**) parallels several similar reactions of isocyanides with pendant nucleophiles. Protonation of the resultant complex **10** releases the oxazole **6** and regenerates the active copper catalyst.

Copper iodide catalyzes a facile conjugate addition–cyclization to isocyano enones that affords oxazoles. The requisite isocyano enones are readily synthesized through two complementary routes that provide access to acyclic and 5–7-membered isocyano enones. A diverse range of carbon and heteroatom nucleophiles efficiently react with these isocyano enones to afford substituted oxazoles ideally functionalized for elaboration into synthetic targets. Mechanistic analysis indicates that the reaction proceeds via a conjugate addition to a copper-activated isocyanide that triggers an enolate cyclization onto the isocyanide to generate the

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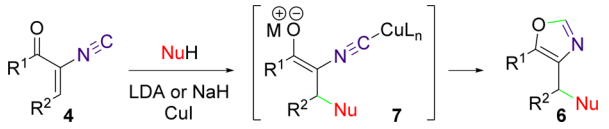
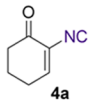
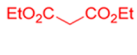
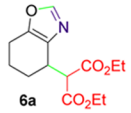
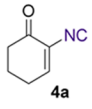
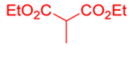
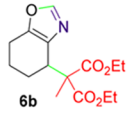
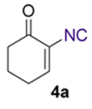
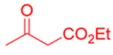
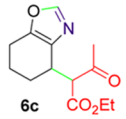
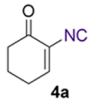
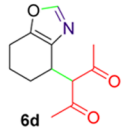
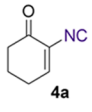
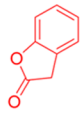
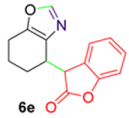
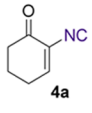
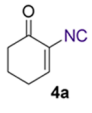
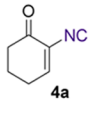
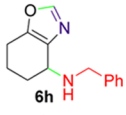
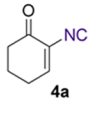
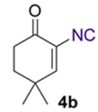
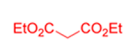
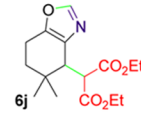
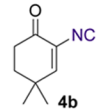
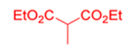
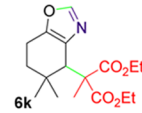
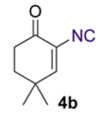
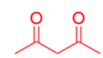
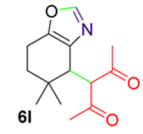
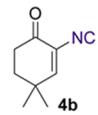
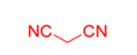
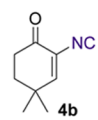
Table 2. Isocyano Enone Addition−Cyclizations[a]



entry	isonitrile	nucleophile	oxazole	yield (%)
1	 4a		 6a	82 (80)[b]
2	 4a		 6b	81
3	 4a		 6c	77[c]
4	 4a		 6d	62 (63)[b]
5	 4a		 6e	64[d]
6	 4a		 6f	57 (55)[b]
7	 4a		 6g	61[d] (58)[b]
8	 4a		 6h	73
9	 4a	TolSH	 6i	85[e]
10	 4b		 6j	51[f]
11	 4b		 6k	62[f]
12	 4b		 6l	46[f]
13	 4b		 6m	64[d,f]
14	 4b		6n	73[f]
15	4c		6o	52
16	4c		6p	57[d]
17	4d		6q	55
18	4d		6r	51

[a]Reaction conditions: **4a** (1 equiv), nucleophile (1.5 equiv), CuI (3 mol %), THF (5.0 mL), LDA (1.1 equiv), 1 h, 0 °C. [b]Yield for a larger scale reaction performed on 0.8 mmol of **4a**. [c]A 7:1 ratio of diastereomers was obtained (determined by 1H NMR). [d]NaH was used in place of LDA. [e]Performed in the absence of base; with NaH, the yield was 62%. [f]The reaction required 3 h to proceed to completion.

oxazole. The synthesis is modular, rapid, and provides a versatile route into a valuable class of heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01147.

^{1}H and ^{13}C NMR FIDs (ZIP)

Experimental procedures and physical characterizations of the products; ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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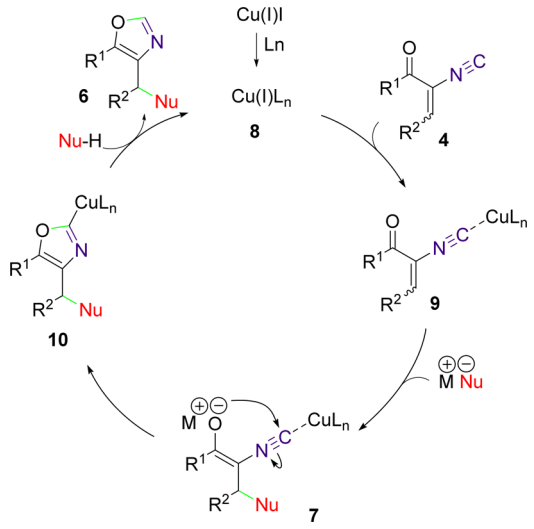
Scheme 3. Cu-Catalyzed Oxazole Formation



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(19) Use of catalytic or substoichiometric base led to incomplete conversion accompanied by unidentified materials. The optimal procedure employed 1.1 equiv of base and 1.5 equiv of nucleophile (see Table 2); the excess nucleophile may provide an adventitious proton source.

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(24) Performing the reaction in D_2O as the solvent resulted in deuteration to afford **6t**; see the Supporting Information.

(25) The basic conditions cause partial deprotonation of the malonate in **6t** that leads, upon workup, to a mixture of mono- and dideuterated oxazoles. Correspondingly, attempts to trap the cuprated oxazole with benzoyl chloride, TMSCl, and iodomethane before protonation were unsuccessful.

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