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Synthesis of 1,6-dihydropyrimidines via copper-catalyzed multistep cascade reactions between *O*-propargylic aldoximes and isocyanates

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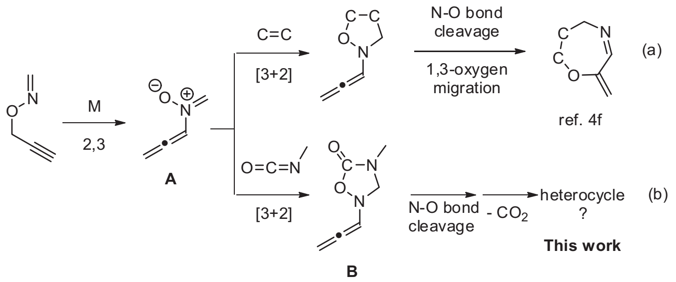
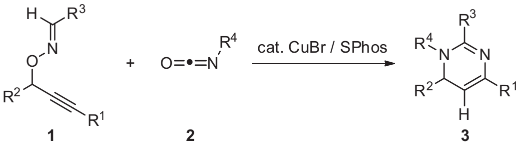
ABSTRACT

Multi-step cascade reactions of *O*-propargylic oximes with isocyanates were carried out in the presence of copper catalysts to afford the corresponding 1,6-dihydropyrimidines in good yields. The multi-step reactions consisted of a 2,3-rearrangement, a [3+2] cycloaddition, decarboxylative ring opening involving a 1,4-hydrogen shift, and a 6π-electrocyclization.

Multi-step cascade reactions have been proven to provide highly efficient transformations in the synthesis of highly elaborate molecules starting from readily available compounds in a single operation.[1] The attractive feature of such methodology can be attributed to the continuous generation of reactive and often elusive intermediates that are kinetically or thermodynamically unstable and/or difficult to prepare.[1] In many cases, such cascade reactions can be triggered by π-acidic metal catalysts that can generate the reactive species in the initial step, under mild reaction conditions, under high tolerances of various functional groups.[2,3] Recently, we reported that *N*-allenylnitrone intermediate **A** can be efficiently generated from *O*-propargylic oximes via π-acidic copper-catalyzed 2,3-rearrangement (Scheme 1).[4] More recently, we carried out the intermolecular cascade reactions involving electron-deficient olefins such as maleimides and fumaric acid esters (Scheme 1a).[4f] The reactions proceeded via a [3+2] cycloaddition between *N*-allenylnitrone **A** and the olefin, followed by a N–O bond cleavage resulting in a 1,3-oxygen migration. In contrast, we envisioned that the sequence of [3+2] cycloaddition/N–O bond cleavage should proceed differently for reactions involving isocyanates as the dipolarophile because *N*-allenyloxadiazolidinone species **B** would favor the liberation of CO_2 rather than undergo a 1,3-oxygen migration (Scheme 1b).[5,6] Herein, we report on the copper-catalyzed reactions of *O*-propargylic aldoximes **1** and isocyanates **2**, in which the multi-step cascade sequence proceeded via a 2,3-rearrangement, a [3+2] cycloaddition, decarboxylative ring opening involving a 1,4-hydrogen migration, and a 6π-electrocyclization, to afford the corresponding 1,6-dihydropyrimidines **3** in good yields (Eq. 1).



Scheme 1. [3+2] Cycloaddition followed by N–O bond cleavage for *N*-allenylnitrone intermediate **A** with (a) olefins and (b) isocyanates (present work).



(1)

Initially, the reaction conditions were optimized using (*E*)-**1a** and *N*-(*p*-toluenesulfonyl)isocyanate **2a** (1.2 equiv), as summarized in Table 1. The reaction was carried out in 1,2-dichloroethane

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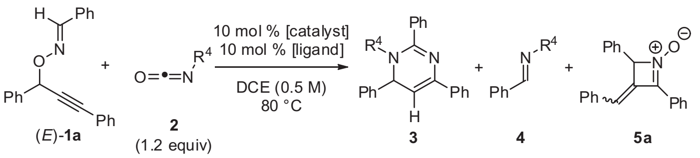
Table 1
Optimization of the reaction conditions

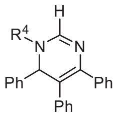


2a (R^4 = Ts)
2b (R^4 = p-$FC_6H_4SO_2$)
2c (R^4 = Bz)
2d (R^4 = p-$O_2NC_6H_4$)

3a (R^4 = Ts)
3b (R^4 = p-$FC_6H_4SO_2$)
3c (R^4 = Bz)
3d (R^4 = p-$O_2NC_6H_4$)

	Catalyst	Ligand	**2**	Time (h)	Yield[a] (%)		
					3	**4**	**5**
1	CuCl	None	**2a**	7	44	15	12
2	CuBr	None	**2a**	5	43	21	6
3	CuI	None	**2a**	21	42	18	5
4	$[CuCl(cod)]_2$[b]	None	**2a**	2	33	25	7
5	$Cu(OAc)_2$	None	**2a**	4	45	8	13
6	$[Cu(CH_3CN)_4]PF_6$	None	**2a**	2	36	20	<1
7	none	None	**2a**	48[c]	<1	4	<1
8	CuBr	None	**2b**	12	24	36	6
9	CuBr	None	**2c**	48	<1	<1	<1
10	CuBr	None	**2d**	10	10	6	25
11	CuBr	P*t*Bu_3	**2a**	6	48	19	6
12	CuBr	PCy_3	**2a**	6	45	18	9
13	CuBr	SPhos	**2a**	12	51	16	7
14	CuBr	PPh_3	**2a**	23	33	18	24
15	CuCl	SPhos	**2a**	24	40	13	<1
16	$Cu(OAc)_2$	SPhos	**2a**	12	44	9	14
17[d]	CuBr	SPhos[e]	**2a**	18	58[f]	16	<1

[a] The yields were determined by ^1H NMR using dibromomethane as an internal standard.
[b] 5 mol %.
[c] 65% of **1a** was recovered.
[d] 0.25 M.
[e] 11 mol % of SPhos was used.
[f] 9% of **6a** was obtained.



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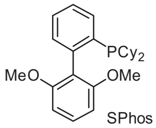
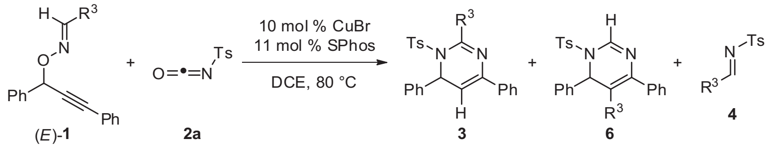


Table 2
Substitution effects at the oxime moiety[a]



	1	R^3	Time (h)	Product (% yield)		
				3[b]	**6**[c]	**4**[c]
1	**1b**	p-$F_3CC_6H_4$	24	**3e** (39)	**6e** (4)	**4e** (21)
2	**1c**	p-ClC_6H_4	14	**3f** (51)	**6f** (7)	**4f** (18)
3	**1a**	Ph	18	**3a** (56)	**6a** (8)	**4a** (16)
4	**1d**	p-$MeOC_6H_4$	12	**3g** (52)	**6g** (21)	**4g** (11)
5	**1e**	Cy	6	**3h** (30)	–	**4h** (17)

[a] The reactions of (*E*)-**1** (0.20 mmol) and *N*-tosylisocyanate **2a** (0.24 mmol) were carried out in the presence of CuBr (10 mol %) and SPhos (11 mol %) in 1,2-dichloroethane (0.8 mL) at 80 °C.
[b] Isolated yields.
[c] The yields were determined by ^1H NMR using dibromomethane as an internal standard.

(DCE), in the presence of CuBr (10 mol %), at 80 °C to afford 2,4,6-triphenyl-1-tosyl-1,6-dihydropyrimidine **3a** (43% yield), along with *N*-tosylbenzaldimine **4a** (21% yield), and the four-membered cyclic nitrone **5a** (6% yield) (entry 2).[7] Cu(I) and Cu(II) salts such as CuCl, CuI, and $Cu(OAc)_2$ exhibited comparable catalytic activities, whereas the use of $[CuCl(cod)]_2$ or $[Cu(CH_3CN)_4]PF_6$ resulted in a lower yield (entries 1–6). The use of transition metal salts such as AgOTf, AuCl, $PtCl_2$, and $InCl_3$ did not promote the present reaction (See Supporting information). The reaction in the absence of copper catalysts did not afford the desired product **3a** at