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Synthesis of 4-methylene-4*H*-benzo[*d*][1,3]thiazines *via* a tandem reaction of 1-(2-alkynylphenyl)ketoximes with Lawesson's reagent†

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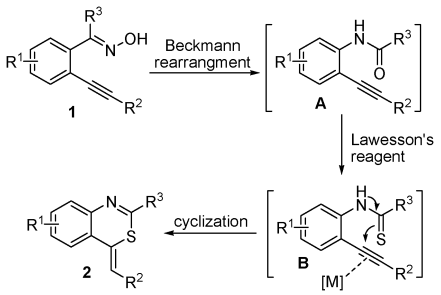
1-(2-Alkynylphenyl)ketoximes react with Lawesson's reagent catalyzed by $InCl_3$ and cyanuric chloride leading to 4-methylene-4*H*-benzo[*d*][1,3]thiazines in good yields. This tandem reaction proceeds with high efficiency through Beckmann rearrangement, thioamide formation, and intramolecular nucleophilic cyclization.

The Beckmann rearrangement of ketoximes is a fundamental synthetic transformation, which has been used as an efficient tool for amide formation.[1] To date, many catalysts including metal salts and organocatalysts have been employed in this transformation.[2] For example, in 2005 Yamamoto and co-workers described a Beckmann rearrangement under reflux in acetonitrile or nitromethane using 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) as an effective organocatalyst (co-catalyzed by either HCl or $ZnCl_2$).[2h]

The construction of heterocyclic systems is of continuing interest in the field of organic chemistry, due to their important place among biologically active natural products and synthetic materials.[3] The 4*H*-benzo[*d*][1,3]thiazine core can be found in many compounds with promising biological activities.[4] Moreover, compounds with this subunit have found application in electroluminescent devices.[4] Among the family of 4*H*-benzo[*d*][1,3]thiazines, 4-methylene-4*H*-benzo[*d*]-[1,3]thiazine is particularly appealing since this kind of compound could be further elaborated to form diverse 4*H*-benzo[*d*]-[1,3]thiazines. In the past few years, we have been involved in the preparation of natural product-like compounds *via* cascade reactions,[5] which are attractive approaches for the efficient generation of complex molecules.[6] During our studies, we were convinced that 2-alkynylbenzaldoxime is a versatile substrate for *N*-heterocycles generation.[7,8] For instance, indole derivatives could be generated *via* a multicatalytic one-pot Beckmann rearrangement/intramolecular cyclization/halogenation reaction of 1-(2-alkynylphenyl)ketoxime.[7a] Inspired by the advancement of the Beckmann rearrangement and our efforts toward improved syntheses of nitrogen-containing heterocycles, we envisioned that 1-(2-alkynylphenyl)ketoxime could be used as a substrate for the generation of 4-methylene-4*H*-benzo[*d*]-[1,3]thiazines. The proposed synthetic route is described in Scheme 1. We anticipated that with a suitable catalyst, a Beckmann rearrangement of 1-(2-alkynylphenyl)ketoxime **1** would occur first to form an amide intermediate **A**. It is well known that benzamide can be easily transformed to benzothioamide in the presence of Lawesson's reagent.[9] Furthermore, Lawesson's reagent was employed in the formation of 2*H*-thiopyrans in a regioselective one pot thionation–[4 + 2]-cycloaddition sequence.[9e] Thus, intermediate **A** would react with Lawesson's reagent leading to thioamide **B**. In the presence of a suitable metal catalyst, the triple bond would be activated. This formed metal-complex renders the carbon–carbon unsaturated bond moiety electrophilic, which triggers an intramolecular attack by the sulfur nucleophile, giving rise to the desired 4-methylene-4*H*-benzo[*d*][1,3]thiazine **2**. Accordingly, this proposed pathway incorporating Beckmann rearrangement, thioamide formation, and intramolecular cyclization in a one-pot process for the formation of 4-methylene-4*H*-benzo[*d*][1,3]-thiazines seemed feasible. To validate this hypothesis, we started to explore the possibility of the transformation shown in Scheme 1.

We began by investigating the reaction of 1-(2-alkynylphenyl)ketoxime **1a** with Lawesson's reagent (Table 1). Since the Beckmann rearrangement works efficiently in the presence of a catalytic amount of cyanuric chloride with an acid co-catalyst,[2h] the initial studies were performed by using cyanuric chloride (10 mol%) and $InCl_3$ (10 mol%) as the co-catalyst.[7a]



Scheme 1 Synthesis of 4-methylene-4*H*-benzo[*d*][1,3]-thiazines *via* a cascade reaction of 1-(2-alkynylphenyl)ketoxime with Lawesson's reagent.

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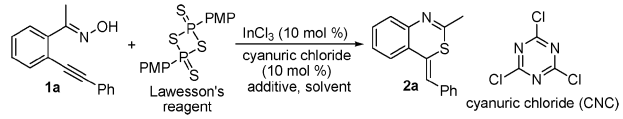
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra of compounds **2**. CCDC 826316. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12937f

Table 1 Initial studies for the tandem reaction of 1-(2-alkynylphenyl)-ketoxime **1a** with Lawesson's reagent



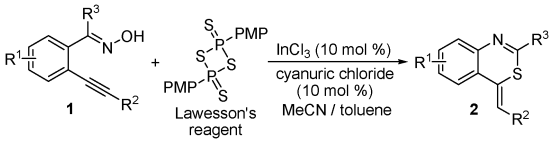
Entry	Additive	Solvent	T/°C	Yield[a] (%)
1	CuI	MeCN	120	42
2	AgOTf	MeCN	120	32
3	$PdCl_2$	MeCN	120	61
4	$PdCl_2(MeCN)_2$	MeCN	120	72
5	—	MeCN	120	72
6	^{t}BuOK	MeCN	120	40
7	Cs_2CO_3	MeCN	120	Trace
8	DBU	MeCN	120	Complex
9	K_3PO_4	MeCN	120	Trace
10	—	Toluene	120	71
11	—	THF	120	34
12	—	1,4-Dioxane	120	24
13	—	EtOH	120	Complex
14	—	DMF	120	Complex
15	—	MeCN/toluene[b]	80 to 120	80
16	—	MeCN/toluene[b]	rt	Trace

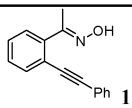
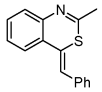
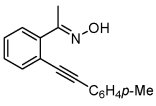
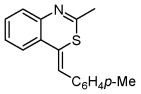
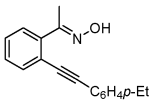
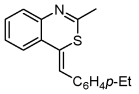
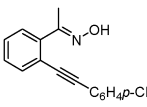
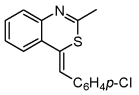
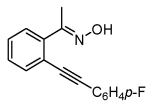
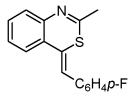
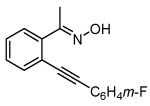
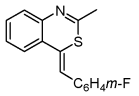
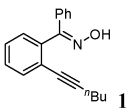
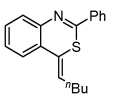
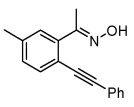
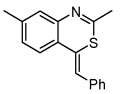
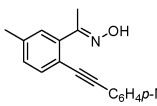
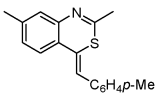
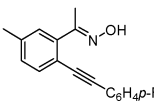
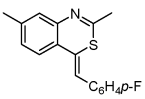
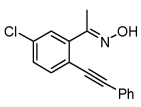
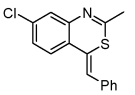
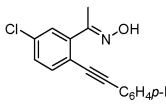
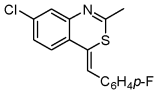
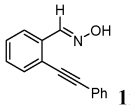
[a] Isolated yield based on 1-(2-alkynylphenyl)ketoxime **1**. [b] MeCN/toluene (v/v: 1 : 2).

At the outset, different metal salts were tested as additives since a metal catalyst would be necessary to activate the triple bond for subsequent intramolecular cyclization. To our delight, the expected product **2a** was isolated in 42% yield when the reaction took place in MeCN at 120 °C in the presence of copper(I) iodide as an additive (Table 1, entry 1). Silver(I) and palladium(II) salts were examined in the meantime (Table 1, entries 2–4), and a good yield was obtained when $PdCl_2(MeCN)_2$ was added to the reaction system (72% yield). However, a blank experiment without the addition of metal additive indicated that $InCl_3$ was an effective catalyst in the Beckmann rearrangement as well as in the intramolecular cyclization process (Table 1, entry 5). No further improvement was observed when organic or inorganic bases were added (Table 1, entries 6–9). Further screening of solvents showed that the reaction worked well in a mixed solvent of MeCN and toluene, which gave rise to the corresponding product **2a** in 80% yield (Table 1, entry 15). However, only a trace amount of product was detected when the reaction occurred at room temperature (Table 1, entry 16). The reactivity was diminished with lower yield and prolonged reaction time when the catalytic amount of cyanuric chloride and $InCl_3$ was reduced to 5 mol% (data not shown in Table 1).

Next, we examined the scope of this tandem reaction under the optimized conditions (10 mol% of cyanuric chloride, 10 mol% of $InCl_3$, MeCN/toluene). The results are shown in Table 2. Most reactions proceeded smoothly to give rise to the corresponding products in moderate to good yields. For instance, 1-(2-alkynylphenyl)ketoxime **1b** reacted with Lawesson's reagent, leading to the desired 4-methylene-4*H*-benzo[*d*][1,3]thiazine **2b** in 96% yield (Table 2, entry 2). Reactions of substrates with a 4-ethylphenyl, 4-chlorophenyl, or 4-fluorophenyl group attached to the triple bond afforded the expected products in good yields as well (Table 2, entries 3–5). A reasonable yield (61%) was obtained when 1-(2-alkynylphenyl)ketoxime **1g** with an alkyl group

Table 2 Tandem reactions of 1-(2-alkynylphenyl)ketoximes with Lawesson's reagent



Entry	Substrate	Product	Yield[a] (%)
1	 **1a**		80 (**2a**)
2	 **1b**		96 (**2b**)
3	 **1c**		73 (**2c**)
4	 **1d**		80 (**2d**)
5	 **1e**		71 (**2e**)
6	 **1f**		40 (**2f**)
7	 **1g**		61 (**2g**)
8	 **1h**		50 (**2h**)
9	 **1i**		70 (**2i**)
10	 **1j**		64 (**2j**)
11	 **1k**		66 (**2k**)
12	 **1l**		45 (**2l**)
13	 **1m**	—	Trace

[a] Isolated yield based on 1-(2-alkynylphenyl)ketoxime **1**.

attached to the C≡C triple bond was used as a reactant (Table 2, entry 7). Other 1-(2-alkynylphenyl)ketoximes with a chloro or methyl group attached to the aromatic ring were examined in the meantime, and all reactions performed well to afford the desired product **2** in moderate yield (Table 2, entries 8–12). Additionally, the structure of 4-methylene-4*H*-benzo[*d*]-[1,3]thiazine **2j** was unambiguously determined by X-ray crystallography analysis (see the ESI†). However, no desired products were observed when R^3 was replaced by hydrogen (Table 2, entry 13) or trimethylsilyl (data not shown in Table 2).

In conclusion, we have described a tandem reaction of 1-(2-alkynylphenyl)ketoxime with Lawesson's reagent catalyzed by $InCl_3$ and cyanuric chloride, which leads to 4-methylene-4*H*-benzo[*d*][1,3]thiazines in moderate to good yields. This cascade process proceeds with high selectivity through Beckmann rearrangement, thioamide formation, and intramolecular nucleophilic cyclization. Further exploration of other cascade reactions using 1-(2-alkynylphenyl)ketoxime as a substrate is ongoing.

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