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Synthesis of 2-Haloalkylpyridines *via* Cp*RuCl-Catalyzed Cycloaddition of 1,6-Diynes with α-Halonitriles. Unusual Halide Effect in Catalytic Cyclocotrimerization

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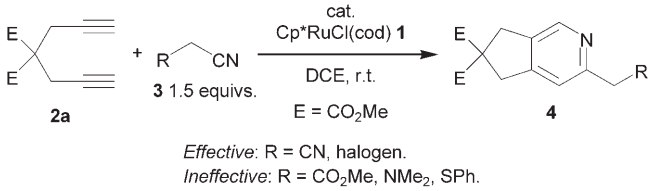
Abstract: In the presence of 2–5 mol % Cp*RuCl (cod), various 1,6-diynes reacted with α-monohalo- and α,α-dihalonitriles at ambient temperature to afford 2-haloalkylpyridines in 42–93% isolated yields. The failure of acetonitrile, *N*,*N*-dimethylaminoacetonitrile, phenylthioacetonitrile, and methyl cyanoacetate as nitrile substrate clearly showed that the α halogen substitution is essential for the present cycloaddition under mild conditions. The cycloaddition of unsymmetrical diynes bearing a substituent on one alkyne terminal gave 2,3,4,6-substituted pyridines exclusively.

Keywords: alkynes; cyanides; cyclotrimerization; pyridines; ruthenium

The transition-metal-mediated [2+2+2] cyclocotrimerization of two alkynes and a nitrile is a powerful and straightforward route to substituted pyridines.[1] Although the catalytic cyclocotrimerization is becoming increasingly important as an environmentally benign process, the pair- and regio-selectivity as well as reaction conditions have remained to be largely improved compared to stoichiometric protocols.[2] In this context, mild and selective catalytic cycloadditions of α,ω-diynes with nitriles were recently achieved by means of a chiral indenylcobalt complex and a nickel N-heterocyclic carbene complex.[3] In particular, the former catalyst proved to be effective toward the asymmetric synthesis of axially chiral pyridines. In addition, novel intramolecular protocols were recently developed to synthesize pyridine-containing macrocycles or 2-aminopyridines.[4]

We have also developed independently the Cp*RuCl-catalyzed cycloadditions of α,ω-diynes with carbon-heteroatom multiple bonds,[5] and found that the dicyanides are exceptional nitrile substrates capable of undergoing cycloaddition even at ambient temperature.[6] In fact, in the presence of 5 mol % Cp*RuCl(cod) **1** (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene), the cycloaddition of dimethyl dipropargylmalonate (**2a**) with malononitrile (**3a**; R = CN) proceeded even at room temperature for 2.5 h to afford bicyclic pyridine **4aa** (R = CN) in 95% yield (Scheme 1). Although one of the two cyano groups remained intact after the reaction, the complete incompetence of acetonitrile provides the possibility of one cyano moiety as a coordinating group. To expand the scope of the nitrile substrate, other nitriles possessing a coordinating group α to the cyano group were further screened (Figure 1). Consequently, methyl cyanoacetate (**3b**; R = CO_2Me), *N*,*N*-dimethylaminoacetonitrile (**3c**; R = NMe_2), and phenylthioacetonitrile (**3d**; R = SPh) were found to be totally ineffective. In striking contrast, chloroacetonitrile (**3e**; R = Cl) underwent cycloaddition with **2a** in the presence of 2 mol % **1** at ambient temperature for 2 h to give rise to chloromethylpyridine **4ae** in 93% isolated yield.[7] This result was quite surprising because trichloroacetonitrile, which underwent cycloaddition with **2a** at 60 °C in our previous study,[5] failed to react at ambient temperature. These facts indicate that the observed reactivity enhancement is *not* ascribed simply to the inductive activation of the cyano group by the chlorine atom. Herein, we report the unprecedented halide effect in the Cp*RuCl-catalyzed cycloaddition of diynes with α-halonitriles.



Scheme 1. Cp*RuCl-catalyzed cycloaddition of dipropargylmalonate with nitriles.

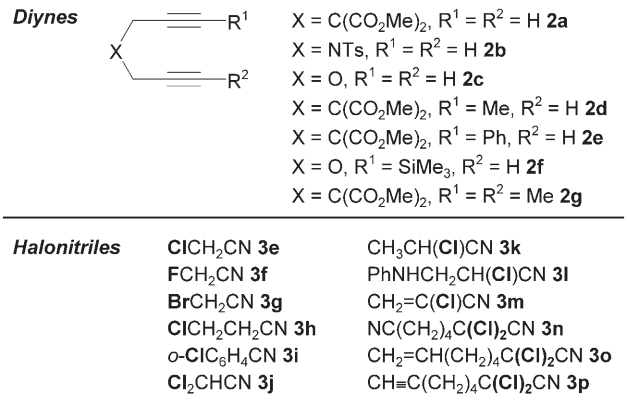


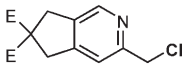
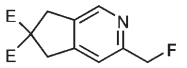
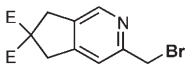
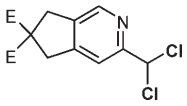
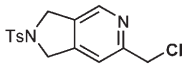
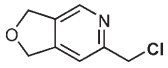
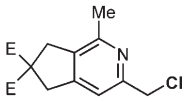
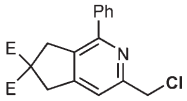
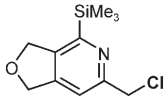
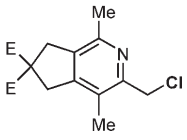
Figure 1. Diynes and halonitriles used in this study.

At the outset of this study, the cycloaddition ability of several halonitriles was examined as summarized in Table 1. Fluoro- and bromo-substituted acetonitriles **3f**, **g** also underwent cycloaddition with **2a** at room temperature, although the yield was diminished for the bromide (runs 1 and 2). This is probably because of the instability of **4ag** toward the substitution of the benzylic bromide. On the other hand, β-chloropropionitrile (**3h**) and *o*-chlorobenzonitrile (**3i**) were totally ineffective, indicative of the importance of the halogenated position on the nitrile. These results are in contrast to those obtained for the cycloadditions of phthalonitrile and succinonitrile giving the corresponding pyridines.[6] Dichloroacetonitrile (**3j**) behaved similarly, and dichloromethylpyridine **4aj** was obtained in 91% yield (run 4). As already mentioned, trichloroacetonitrile did not gave the corresponding product at ambient temperature even with an increased catalyst loading of 5 mol % and longer reaction time of 24 h.

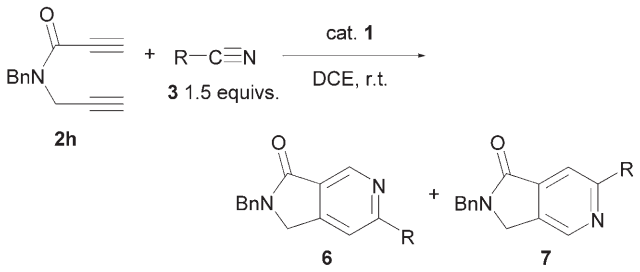
To establish the generality, various diyne substrates were subjected to the cycloaddition with chloroacetonitrile (**3e**). The use of *N*,*N*-dipropargyltosylamide (**2b**) and propargyl ether **2c** led to the formations of pyridine-fused heterocycles **4be** and **4ce** in good yields, although longer reaction time was required for the latter (runs 5 and 6). Gratifyingly, the reactions of unsymmetrical diynes **2d**–**f** resulted in the formation of only single regioisomers **4de**, **4ee**, and **4fe**, in which the methyl, phenyl or trimethylsilyl groups were placed α to the nitrogen atom (runs 7–9). Internal diyne **2 g** also gave rise to fully substituted pyridine **4ge** in 71% yield (run 10).

Next, we explored the cycloaddition of variously substituted α-chloronitriles, and the results are complied in Table 2. 2-Chloropropionitrile (**3k**) and its analogue **3 l** bearing a *N*-phenylamino group were allowed to react with diyne **2a** to furnish pyridines **4ak** and **4al** in good yields (runs 1 and 2). Similarly, 2-chloroacrylonitrile (**3m**) afforded vinylpyridine **4am** in 87% yield (run 3). In the case of dicyanide **3n**, the cycloaddition exclusively took place at the cyano group α to the dichloromethylene, resulting in the formation of cyanoalkylpyridine **4an** in 84% yield (run 4). Moreover, the selective pyridine formations were also accomplished with nitriles **3o** and **3p** possessing an alkene or an alkyne terminal,

Table 1. Cycloadditions of 1,6-diynes **2** with α-halonitriles **3**.[a, b]

Run	Substrates **1**	[mol %]	*t* [h]	**4**	Yield [%]
1	**2a**, **3e**	2	2	**4ae** 	93
2	**2a**, **3f**	2	1	**4af** 	90
3	**2a**, **3 g**	2	3	**4ag** 	42
4	**2a**, **3j**	2	3	**4aj** 	91
5	**2b**, **3e**	2	4	**4be** 	80
6	**2c**, **3e**	2	20	**4ce** 	71
7	**2d**, **3e**	2	3	**4de** 	88
8	**2e**, **3e**	5	6	**4ee** 	80
9	**2f**, **3e**	5	4	**4fe** 	76
10	**2g**, **3e**	2	24	**4ge** 	71

[a] All reactions were carried out with diyne **2** (1 equiv.) and nitriles **3** (1.5 equivs.) in 1,2-dichloroethane at room temperature.
[b] E = CO_2Me.



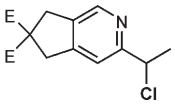
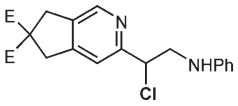
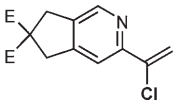
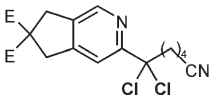
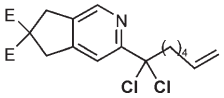
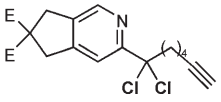
3a R = CH_2CN; 1 mol % **1**, 1 h; 90% yield, **6ha**:**7ha** = 50:50
3e R = CH_2Cl; 2 mol % **1**, 3 h; 84% yield, **6he**:**7he** = 53:47
3j R = $CHCl_2$; 2 mol % **1**, 3 h; 89% yield, **6hj**:**7hj** = 80:20

Scheme 2. Electronic effect on regioselectivity in cycloaddition of amide-tethered diyne.

whereas these unsaturated α,α-dichloronitriles are able to undergo transition-metal-catalyzed atom-transfer radical cyclization.[8] These results clearly ruled out the possibility of radical intermediates generated *via* chlorine atom abstraction for the pyridine formation.

Although the mechanistic details are not clear in this stage, the halonitriles might act as bidentate ligands with both halide and cyano groups coordinating to a cationic ruthenabicycle intermediate.[5,9] When diyne **2a** and chloroacetonitrile (**3e**) were treated with 2 mol % of **1** as well as 5 mol % Et_3NCl, the reaction was completed after 18 h to give rise to a dimer of **2a** together with pyridine **4ae** in 14% and 68% yields, respectively. This result suggests that the higher concentration of chloride ion partially suppressed the formation of the cationic species to result in the unfavorable dimerization of **2a**. In place of the α-haloalkylnitriles, the use of β-chloropropionitrile and *o*-chlorobenzonitrile led to the exclusive formation of the diyne dimer, indicative of the bite angle of these halonitriles being important to suppress the dimerization. To obtain further insight into the present halide effect, we further carried out some experiments with diyne **2h**, in which one of two alkyne moieties is directly connected to the internal carbonyl group (Scheme 2). We previously found that such an unsymmetrical diyne reacted with terminal alkynes, electron-deficient nitriles, and isocyanates to give the corresponding cycloadducts with moderate to high regioselectivity.[5,10] In striking contrast, no regioselectivity was observed for the cycloadditions of **2h** with malononitrile (**3a**) or chloroacetonitrile (**3e**), indicative of the cycloaddition with these nitriles proceeding *via* a different mechanism from the other examples. Moreover, we found that the similar cycloaddition of dichloroacetonitrile (**3j**) exhibited considerable regioselectivity, and the corresponding products **6hj** and **7hj** were obtained in a ratio of 80:20. Consequently, the number of the chlorine substitutions at the α position dramatically alters the reactivity as well as the regioselectivity in the Cp*RuCl-catalyzed cycloaddition with the 1,6-diynes.

Table 2. Synthesis of 2-chloroalkylpyridines **4**.[a,b]

Run	Nitrile	**1** [mol %]	*t* [h]	**4**	Yield [%]
1	**3k**	2, 4	4	**4ak** 	87
2	**3l**	2, 6	6	**4al** 	71
3	**3m**	2, 2	2	**4am** 	87
4	**3n**	2, 10	10	**4an** 	84
5	**3o**	2, 24	24	**4ao** 	76
6	**3p**	2, 24	24	**4ap** 	81

[a] All reactions were carried out with diyne **2a** (1 equiv.) and nitriles **3** (1.5 equivs.) in 1,2-dichloroethane at room temperature.
[b] E = CO_2Me.

In conclusion, we successfully achieved the mild and highly selective synthesis of 2-haloalkylpyridines by means of the Cp*RuCl-catalyzed cycloaddition of diynes with α-halonitriles. To the best of our knowledge, the above described halide effects in catalytic cyclocotrimerization are unprecedented phenomena, although the dramatic influences of halide ligands in transition-metal catalysis have been well documented.[11] Besides, haloalkylpyridines are useful building blocks for substituted pyridines and potential herbicides.[12] The elucidation of the detailed mechanism must wait further study.

Experimental Section

General Procedure for Cp*RuCl-Catalyzed Cycloaddition of Diynes and α-Halonitriles: Synthesis of Pyridine 4ae from 1,6-Diyne 2a and Chloroacetonitrile (3e)

To a solution of chloroacetonitrile (**3e**; 34.0 mg, 0.45 mmol) and Cp*RuCl(cod) (**1**; 2.4 mg, 0.006 mmol) in dry degassed 1,2-dichloroethane (1 mL) was added a solution of diyne **2a** (62.5 mg, 0.3 mmol) in dry degassed 1,2-dichloroethane (2 mL) over 15 min under an argon atmosphere at room temperature. After stirring for 2 h, the solvent was evaporated and the crude product was purified by silica gel flash column chromatography (eluent hexane:AcOEt = 2:1) to give **4ae** as a colorless oil; yield: 79.1 mg (93%). The spectral data for **4ae** were as reported.[7]

Supporting Information

General considerations, general procedure for Cp*RuCl-catalyzed cycloaddition of diynes and α-halonitriles, and characterization data of pyridines **4af**, **4ag**, **4aj**, **4be**, **4ce**, **4de**, **4ee**, **4fe**, **4ge**, **4ak**, **4al**, **4am**, **4an**, **4ao**, **4ap**, **6ha/7ha** and **6hj/7hj**.

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