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A Ruthenium Complex-Catalyzed Cyclotrimerization of Halo-
diyynes with Nitriles. Synthesis of 2- and 3-Halopyridines

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Abstract: Monohalo- and dihalodiyynes efficiently undergo [2+2+2] cycloaddition with nitriles in the presence of a catalytic amount of the ruthenium complex Cp*RuCl(cod) (10 mol%) to afford the corresponding halopyridines under ambient conditions in good isolated yields (up to 90%). The halopyridines are formed as two separable regioisomers. This is the first example of a direct synthesis of halopyridines from haloalkynes and nitriles.

Keywords: alkynes; cyclotrimerization; homogeneous catalysis; nitrogen heterocycles; ruthenium

Pyridines and their more complex derivatives are an important class of heteroaromatic compounds. Substances possessing the pyridine framework are found in numerous branches of chemistry. [1] Out of many synthetic methods used for their preparation, [2] perhaps the simplest and the most efficient, is catalytic cyclotrimerization of alkynes with nitriles by using transition metal compounds. [3]

Although a number of catalytic protocols have been developed, there is still a considerable space to explore cyclotrimerization for hitherto untapped combinations of alkynes and nitriles. In this respect, it would be desirable to develop a procedure allowing synthesis of pyridines possessing a reactive functional group on the pyridine scaffold that would allow further transformations. It would be synthetically interesting if a cyclotrimerization would allow formation of halopyridines by a catalytic reaction of haloalkynes with nitriles.

As far as the cyclotrimerization of chloro-, bromo- and iodoalkynes is concerned, they can efficiently react with alkynes in cyclotrimerization processes to give the corresponding halobenzenes. These processes include: (i) Ru- or Co-catalyzed reactions of monohalo- and diiododiyynes with alkynes to iodobenzenes that were further functionalized by cross-coupling reactions; [5] (ii) Ru- or Rh-catalyzed cyclotrimerization of monobromodiynes with alkynes as a route to new potentially selective inhibitors of tyrosine kinase 2; [6] (iii) Ru-catalyzed cyclotrimerization of a highly substituted chlorodiyne and alkyn during the course of the sporolide B synthesis. [7] Although, a Ru-complex catalyzed cycloaddition of haloalkynes with nitrite oxides and organic azides has been recently described, [8] their cyclotrimerization with nitriles providing halopyridines, interestingly, has not been reported so far (to the best of our knowledge). Our interest in cyclotrimerization of the halodiyynes with the nitriles stemmed for the fact that this procedure could be used as an important step in syntheses of pyridines and derivatives thereof. They can be used in numerous homogeneous catalytic racemic or enantioselective processes as ancillary ligands and their derivatives (e.g., N-oxides, etc.) as Lewis basic organocatalysts. [10,11] One such an example is Bolm’s ligand, which has the bipyridine scaffold. Therefore, it would be thus desirable to develop the cyclotrimerization of halodiyynes with alkynes to substituted halopyridines, because they could serve as convenient intermediates for synthesis of bipyridines and other types of pyridine-based ligands.

At the outset, the cyclotrimerization of iododiyne 1a with ethyl cyanoformate 2a as model compounds was screened under different conditions, to explore a possibility for the preparation of iodopyridines (Table 1). The reaction was carried out in dichloroethane (DCE) in the presence of a large excess of cyanoformate (20 equiv.) to ensure high conversion by using the previously reported conditions for Ru-catalyzed cyclotrimerization of iodoalkynes with alkynes.
 Gratifyingly, the cyclotrimerization took place and provided three products 3aa, 4aa, and 5aa in 23, 33, and 3% isolated yields (59% combined yield) (entry 1). Compounds 3aa and 4aa were regioisomers formed by different insertion pathways into the intermediate ruthenacycle, whereas 5aa possessed chlorine instead of iodine. The formation of this compound was a bit puzzling, but subsequent investigation could reveal the origin of its formation (vide infra). Then, the effects of the nitrile/alkyne ratio, catalyst load and solvent on the course of the reaction were explored. The obtained results (entries 2–5) indicated the 2/1 nitrile/diyne ratio to be optimal giving products in 76% combined yield. Using 10 mol% of the catalyst seemed to be optimal for high yields of the products (entries 6–8). As far as the reaction medium is concerned, cyclotrimerization proceeded to give high isolated yields of the products (77–89%) in dichloromethane, tetrahydrofuran, chloroform, and cyclopentyl methyl ether (entries 9–12). Attempts to induce the cyclotrimerization with Co or Rh catalysts were not successful, despite the fact that these catalysts were shown to catalyze the cyclotrimerization of iodoalkynes with alkynes. In both cases the reaction did not take place; moreover, slight decomposition of iodoalkyne 1a was observed (entries 13 and 14). Although speculative, their inactivity may arise from a competitive oxidative addition of the reactive spC–halogen bond that might oxidatively add to these compounds providing catalytically inactive species. With respect to the above described results, the following conclusions could be made on the optimal reaction conditions: (i) 2/1 nitrile/alkyne ratio, (ii) 10 mol% of Cp*RuCl(cod), (iii) chlorinated solvents as the reaction medium, (iv) reaction temperature of 20°C.

The structure of the regioisomers was unequivocally confirmed by single crystal X-ray analyses of 3aa and 4aa (Figure 1 and Figure 2).

Then the efficacy of the Ru-catalyzed cyclotrimerization of bromo-1b and chlorodiynes 1c with cyanoacetate 2a was examined for comparison under the optimized conditions (Table 2). The reaction with bromodiyne 1b proceeded with full conversion of the starting material and provided a mixture of 3ba, 4ba, and 5aa in a combined 91% isolated yield (entry 2). The use of the chlorodiyne 1c furnished 3ca and 4ca in a lower yield of 72% (entry 3). Obviously, the use of the bromo derivative 1b was advantageous with respect to yields of products. Attempts to increase the reaction rate of cyclotrimerization of 1b by using AgOTf to generate a cationic complex or to sup-

### Table 1. Catalytic cyclotrimerization of 1a with 2a under different conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2a (equiv.)</th>
<th>Catalyst[a]</th>
<th>(mol%)</th>
<th>Time [h]</th>
<th>Solvent[b]</th>
<th>3aa</th>
<th>4aa</th>
<th>5aa</th>
<th>Combined</th>
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<td>–</td>
</tr>
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<td>2</td>
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<td>traces</td>
<td>traces</td>
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</table>

[a] Ru = Cp*RuCl(cod); Co = CpCo[P(OEt)3]2(diethylfumarate); Rh = [Rh(cod)]BF4, (R)-BINAP. Reactions were run at 20°C unless otherwise noted.
[b] DCE = 1,2-dichloroethane, DCM = dichloromethane, CPME = cyclopentyl methyl ether.
[c] Isolated yields unless otherwise noted; nr = no reaction.
[d] Yields determined by 1H NMR.
[e] The reaction was run at 100°C.
[f] The reaction was run at 20°C (20 h) and then at 50°C (16 h).
press formation of $5\text{aa}$ by addition of $\text{Bu}_4\text{NBr}$ did not meet with success. The former resulted in the formation of a complex reaction mixture, in which only traces of the desired products were detected (entry 4). The latter had only a marginal if any effect on the product distribution (entry 5).

In order to elucidate the formation of the chloro derivatives, the following experiments were carried out. Firstly, $3\text{aa}$ (containing approximately 12% of $5\text{aa}$) was mixed with an equimolar amount of $\text{Cp}^*\text{RuCl(cod)}$ in deuterated dichloromethane and stirred at 20 °C. According to the $^1\text{H}$ NMR analysis of the reaction mixture (thanks to characteristic signals of $3\text{aa}$ and $5\text{aa}$) already 50% of $3\text{aa}$ was converted to $5\text{aa}$ after 10 h while after 10 days the conversion was 80% (see Figure SI-1 and Figure SI-2 in the Supporting Information).

A halogen exchange reaction is a synthetically interesting reaction proceeding in the presence of various transition metal compounds, including ruthenium complexes.\[13\] The Ru-catalyzed halogen exchange has been observed with triflates ($[\text{Cp}^*\text{Ru(MeCN)}_3]\text{OTf}$ and $\text{LiBr}$)\[14\] and acyl halides ($\text{CpRuCl(PPh}_3)_2$ with $\text{Me(OCO)}X$, $X=\text{Cl}$, Br, I).\[15\] As for the reaction mechanism of the Ru-catalyzed halide exchange, two hypotheses have been proposed. The first one assumes the halogen exchange to proceed via oxidative addition forming a cationic Ru(IV) 18 electron complex followed by ligand exchange ($\text{TfO}^-$ for $X^-$) and subsequently undergoing reductive elimination. The second one, based on experimental results and DFT calculations, proposes the course of the reaction to proceed via a radical pathway. Since thermochemical data clearly show that in 2-chloropyridine the C–Cl bond ($\text{BDE (C–Cl)} = 90.5 \text{ kcal mol}^{-1}$)\[16\] is much stronger than the C–I bond in 2-iodopyridine ($\text{BDE (C–I)} = 63.1 \text{ kcal mol}^{-1}$),\[17\] we assume this difference in

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### Figure 1. ORTEP drawing of $3\text{aa}$ with 30% thermal ellipsoids.

![Figure 1](image1.png)

### Figure 2. ORTEP drawing of $4\text{aa}$ with 30% thermal ellipsoids.

![Figure 2](image2.png)

### Table 2. Ru-catalyzed cyclotrimerization of diynes $1$ with nitrile $2a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$1$ (equiv.)</th>
<th>Time [h]</th>
<th>Additives</th>
<th>$3$</th>
<th>Yield [%]$^{[a]}$</th>
<th>$5\text{aa}$$^{[b]}$</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{ia}$</td>
<td>37</td>
<td>–</td>
<td>$\text{3aa}$</td>
<td>29</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>$\text{ib}$</td>
<td>21</td>
<td>–</td>
<td>$\text{3ba}$</td>
<td>40</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>$\text{ic}$</td>
<td>21</td>
<td>–</td>
<td>$\text{3ca}$</td>
<td>36</td>
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<td>–</td>
</tr>
<tr>
<td>4</td>
<td>$\text{ib}$</td>
<td>39</td>
<td>AgOTf</td>
<td>$\text{3ba}$</td>
<td>traces</td>
<td>36</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>$\text{ib}$</td>
<td>20</td>
<td>Bu$_4$NBr</td>
<td>$\text{3ba}$</td>
<td>31</td>
<td>39</td>
<td>2</td>
</tr>
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</table>

$^{[a]}$ Isolated yields.

$^{[b]}$ The compound’s structure is the same as that of $3\text{ca}$.
bond strength to be the driving force of the reaction.\textsuperscript{[18]} To verify this assumption, 2-iodopyridine was stirred with Cp*RuCl(cod) in deuterated dichloromethane. The exchange proceeded in the same fashion, but the reaction rate was much faster: 50% conversion to 2-chloropyridine was observed already after 5 hours and 90% conversion after 48 h (see Figure SI-3 and Figure SI-4 in the Supporting Information). However, attempts to carry out the iodine-chlorine exchange under catalytic conditions [10 mol\% \text{Cp*RuCl(cod)}] in the presence of LiCl (THF, MeOH, DMF) or Me$_4$NCl (DCE/MeOH) in various solvents were not met with success and only traces (~1–2\%) of the desired 2-chloropyridine were observed after prolonged reaction time (1 week) even if the temperature was increased to 50°C.

Having elucidated the formation of the chloro derivatives, we decided to proceed with an assessment of the reaction scope and the cyclotrimerization of various nitriles 2 with 1b was undertaken (Table 3). Although the reaction with cyanoformate 2a proceeded to give high yields of products (Table 2, entry 2), the reactions with other nitriles gave variable yields. Thus the reaction with cyanoacetate 2b at 20 or 50°C did not yield the desired products. On the other hand, the use of highly electron-deficient malononitrile 2c at 20°C provided a mixture of 3bc (59\%) and 4bc (13\%) yield along with minor amount of 5ac (2\%) (entry 1). A possible product of the double cyclotrimerization was not observed. A reaction of 1b with benzonitrile 2d and 4-chlorobenzonitrile 2e did not provide the expected products at 20 or 50°C. Interestingly, reaction with 3,5-difluorobenzonitrile 2f and 2,4,6-trifluorobenzonitrile 2g gave opposite results. The former gave rise to 3bf and 5af in 16\% and 3\% isolated yields, respectively (entry 2), whereas 4bf was formed just in traces (~1\%). Gratifyingly, the use of highly electron-deficient nitrile 2h at 20 or 50°C pro-

Table 3. Ru-catalyzed cyclotrimerization of various nitriles 2 with 1b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R =</th>
<th>Temp. [°C]</th>
<th>Time [h]</th>
<th>Yield [%]</th>
<th>Combined</th>
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<td>20</td>
<td>13</td>
<td>3bc 59</td>
<td>4bc 13</td>
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<td>2</td>
<td>2f</td>
<td>20</td>
<td>143</td>
<td>3bf 16</td>
<td>4bf traces</td>
</tr>
<tr>
<td>3</td>
<td>2h</td>
<td>20</td>
<td>40</td>
<td>3bh 30</td>
<td>4bh nd\textsuperscript{[b]}</td>
</tr>
<tr>
<td>4</td>
<td>2i</td>
<td>20</td>
<td>69</td>
<td>3bi 31</td>
<td>4bi 12</td>
</tr>
<tr>
<td>5</td>
<td>2j</td>
<td>50</td>
<td>10</td>
<td>3bj 31</td>
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<tr>
<td>6</td>
<td>2l</td>
<td>20</td>
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<td>8</td>
<td>2n</td>
<td>20</td>
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<td>3bn 51</td>
<td>4bn 13</td>
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\textsuperscript{[a]} Isolated yields.
\textsuperscript{[b]} nd = not detected.
\textsuperscript{[c]} An inseparable mixture of regioisomers. The ratio was determined from $^1$H NMR.
vided 3bh in 30% yield, along with a minor amount of 5ah (5%) (entry 3). Interestingly, formation of regioisomer 4bh was not detected. The use of electron-deficient nitrides such as 3,5-bis(trifluoromethyl)benzoxazetidine 2i and 4-nitrobenezonitrile 2j resulted in the formation of both regioisomers. The former furnished 3bi and 4bi in 31% and 12% isolated yields along with 5ai (5%) (entry 4). The latter furnished 3bj and 4bj in 27% and 5% isolated yields along with 5aj (6%). Carrying out the reaction at 50°C had only marginal effect on the overall yields of products and provided 3bj, 4bj, and 5aj in 31, 8, and 5% yields, respectively (entry 5). Interestingly, the reaction with 1,4-dicyanobenzene 2k gave rise only to traces of the expected products. Then our attention turned to acyl cyanides such as acetyl cyanide 2l, pivaloyl cyanide 2m and benzyol cyanide 2n. In all cases the reaction proceeded at 20°C to give mixtures of both regioisomers in good isolated yields (entries 6, 7, and 8). Formation of chloro derivatives 5ai-5an was observed in the usual extent (1–3%). The above mentioned results indicate that only strongly electron-deficient nitrides enter this type of cyclotrimerization reaction. It should be also noted that somewhat better results, that is, up to 15% higher yields, were obtained with new batches of the catalyst, indicating that the course of the reaction with respect to conversions and yields could be affected by the catalyst quality.

The scope of the reaction with respect to diynes was tested afterwards (Table 4). Cyclotrimerizations were carried out with 1-bromo-1H-1,4-dicyanobenzene 2k, 1-bromo-1H-phenyl-1,7-octadiyne, 1H-1,6-heptadiyne, and 1-bromo-1H-1,7-octadiyne 1k with 2a proceeded at 20°C or at 50°C. Only traces of the trimethylsilyl group (5%)(entry 4) were detected (entry 6). On the other hand, cyclotrimerization of diethyl 2-(3-bromoprop-2-ynyl)-2-(prop-2-ynyl)malonate 1j with 2a proceeded to give 3ja and 4ja in 31 and 38% yields, respectively (entry 7). Cyclotrimerizations of 1-bromo-1H-1,7-octadiyne 1k with 2a did not give the desired products (entry 8). These results are not so much surprising since a similar phenomenon had been ob-

Table 4. Ru-catalyzed cyclotrimerization of various diynes 1 with 2a.

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<th>Entry</th>
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<th>R</th>
<th>Temp. [°C]</th>
<th>Time [h]</th>
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<th>Yield [%][b]</th>
<th>4</th>
<th>Yield [%][c]</th>
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<td>4ka</td>
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<td>5ka</td>
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[a] Isolated yields.
[b] nd = not detected, nr = no reaction.
[c] An inseparable mixture of regioisomers. The ratio was determined from 31HNMR.
[d] Homocyclotrimerization of the starting diyne was observed.
served in Ru,[46] as well as in Rh-catalyzed[20] cyclotrimerizations of halodynes previously. It should be noted that in cases of cyclotrimerization of diynes possessing the terminal triple bond (1h, 1i, and 1k) homocyclotrimerization of diynes was observed as an undesirable side reaction (in case of 1k only traces of the benzene product were detected by 1H NMR analysis of the reaction mixture).

Finally cyclotrimerization of 2a with 1,1'-dibromodiynes was screened (Scheme 1). In the case of dibromodiynes 11–1n cyclotrimerization proceeded uneventfully and furnished the desired products 6la–6na in high isolated yields of 83, 81, and 77%, respectively. In all cases also chloro derivatives 5la–5na were formed as minor by-products (2–6%). As expected on the base of previous results (entry 8, Table 4) cyclotrimerization of 1,8-dibromo-1,7-octadiyne 1o did not give the desired product either at 20 or at 50°C.

Last but not least, utilization of the prepared bromopyridines 3ba and 4ba in cross-coupling reactions with 3,5-dimethylphenylboronic acid 6 and vinylboronic acid pinacol ester 7 was briefly screened (Scheme 2). Thus reaction of 3ba with 6 and 7 under the recently reported Suzuki coupling conditions[21] [Pd(PPh3)2Cl2 (10 mol%), CsF, dioxane, H2O, 95°C] provided the expected phenylated and vinylated products 8 and 9 in very good 92 and 79% isolated yields, respectively. Analogously proceeded the reactions with 4ba that gave rise to phenylated and vinylated products 10 and 11 in nice 89 and 83% isolated yields, respectively.

In summary, (i) 1-halo- and 1,7-dibromohexadiynes could be successfully cyclotrimerized with electron-deficient nitriles to the corresponding halopyridines under catalysis of the Ru-complex (10 mol% of the catalyst is required); (ii) the optimal nitrile/alkyne ratio is 2/1; (iii) the optimal reaction temperature is 20°C, in the case of less reactive alkynes/nitriles, 50°C could be used, (iv) the reaction can be run in different solvents such as chloroalkanes or ethers, (v) for the reactions of 1a, 1b, and 1j with 2a a slight preference for 3-halopyridine is observed, whereas for other cases a slight preference for the formation of 2-halopyridines was observed. A brief study regarding cross-coupling reactions of the regioisomeric products was undertaken: both regioisomers reacted almost quantitatively providing basic proof of concept for further functionalization.

**Experimental Section**

Ethyl 4-Iodo-7-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylate (3aa), Ethyl 7-Iodo-4-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylate (4aa), and Ethyl 4-Chloro-7-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylate (5aa)

Into a dried flask containing Cp*RuCl(cod) (7.6 mg, 0.02 mmol) under an argon atmosphere, DCE (1 mL) and nitrile 2a (40 mg, 0.4 mmol) were slowly added. Then diyne 1a (47 mg, 0.2 mmol) dissolved in DCE (1.2 mL) was added during the course of 15 min and the reaction mixture was stirred at 20°C. After the full consumption of the starting diyne (disappearance of the respective spot from TLC analysis), volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradi-
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References


[22] CCDC 1442030 (3aa) and CCDC 1442031 (4aa) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.