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Published paper

Lewis Base Directed Cycloaddition Reactions of 2-Pyrones and Alkynylaluminum Reagents

Damien F. Crépin and Joseph P. A. Harrity*

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, S3 7HF, U.K.
j.harrity@sheffield.ac.uk

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ABSTRACT

In situ generated alkynylaluminum reagents have been utilized in a [4 + 2] cycloaddition with 2-pyrones bearing a Lewis basic donor. The reactions proceed at or below room temperature and with complete regiocontrol. This one-pot method affords diversely substituted aromatic compounds under very mild conditions.

The selective formation of aromatic compounds has attracted considerable interest in synthetic chemistry due to their importance in diverse areas of the chemical industry. Various methods have been developed for their synthesis, mainly including electrophilic or nucleophilic substitution reactions, transition-metal-catalyzed cross-coupling, or C–H bond functionalization of preformed aromatic compounds.1 Another strategy relies on regioselective benzannulation reactions that obviate the need for specific directing groups when incorporating substituents, and a range of such methods have been reported that employ metal promoted or pericyclic reactions.2 As outlined in Figure 1, we have become interested in the potential of the substrate directing group concept3 for promoting such cycloadditions and have reported the implementation of in situ generated alkynyldifluoroboranes toward this end.4 This mild method allows for the formation of diversely substituted aromatic compounds which can easily undergo further functionalization. We envisaged that this method could allow access to other aren-based organometallics by the cycloaddition of alkynes bearing other Lewis acids. In this context, we report herein the use of alkynylaluminum derivatives as new 2π components in a directed [4 + 2] cycloaddition with 2-pyrones.

Figure 1. Lewis base directed cycloaddition of 2-pyrones and alkynes.

Preliminary investigations into the cycloaddition of 2-pyrones and alkynyl dichloroboranes5 proved to be disappointing. These alkynes appeared to be unreactive at low temperature (−78 °C) and served to decompose the pyrones at more elevated temperatures. In contrast however, in situ generated diethyl(phenylethynyl)aluminum 2a reacted with 2-pyrene 3a at ambient temperature to provide

biaryl 4 in high yield. We presume that 4 results from the hydrolysis of intermediate A (vide infra). Similarly, di-methyl(phenylethynyl)aluminum 2a can also be prepared in situ and employed in the cycloaddition with pyrone 3a, affording compound 4 in 82% yield. The importance of the Al-moiety in this reaction was confirmed by reacting 3a with phenylacetylene; we were unable to detect any cycloadduct after heating the substrates at 60 °C over an extended time period.

The optimization of the initial conditions (Table 1, entry 1) was carried out using diethyl(phenylethynyl)aluminum 2a due to the less pyrophoric nature of diethylaluminum chloride relative to the dimethyl-analog. We observed no reactivity upon changing the reaction solvent for THF, or reducing the reaction temperature to 0 °C (entries 2 and 3). However, conducting the reaction in DCE at 0 °C resulted in full conversion after 2 h and 4 was isolated in 59% yield. Moreover, we found that the stoichiometry of diethyl(phenylethynyl)aluminum reagent 2a could be reduced to 1.5 equiv, affording biphenyl 4 in 73% yield when the reaction was conducted at rt (entry 5). Decreasing the temperature to 0 °C gave 4 in a similar yield (entry 6). Finally, we found that pyrone 3a also undergoes the cycloaddition when treated with only 1.1 equiv of alkynylaluminum 2a (entry 7). Under these conditions, 4 was isolated in 69% yield.

We next investigated the scope of the reaction, using 3 equiv of alkynyldiethylaluminum compounds throughout to ensure complete conversion (Table 2). We found that pyrones 3b and 3c, respectively substituted by a thioamide and an ester group, did not undergo the cycloaddition; instead the starting material was recovered in each case (entries 2 and 3). In contrast, pyrones that incorporated various amide groups 3d–f afforded the corresponding cycloadducts 7–9 in good yields (entries 4–6), including substrate 3f that bears a free N–H group. We next looked at a range of N-heteroaromatics in order to establish their potential as directing groups for the cycloaddition of 2a. While pyridine-substituted pyrone 3g gave product 10 in 78% yield (entry 7), we were surprised to recover oxazole and thiazole substituted pyrones 3h and 3i unreacted (entries 8 and 9). Interestingly, when the pyrone is branched at the C2 position of the thiazole instead of position C4 (3j versus 3i), cycloadduct 13 was produced in 70% yield (entry 10). Moreover, imidazole-substituted pyrone 3k was also reactive, affording 14 in 69% yield (entry 11). Finally, we discovered that different

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(6) For examples of the use of dialkyl(aryl)aluminum intermediates in synthesis, see: (a) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. Angew. Chem., Int. Ed. 2008, 47, 8211. (b) Gao, H.; Knochel, P. Synlett 2009, 1321.


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Table 1. Optimization of the [4 + 2] Cycloaddition

<table>
<thead>
<tr>
<th>entry</th>
<th>n equiv of 2a</th>
<th>solvent</th>
<th>temp</th>
<th>time</th>
<th>isolated yield of 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>DCE</td>
<td>rt</td>
<td>1 h</td>
<td>78%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>THF</td>
<td>rt</td>
<td>1 h</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>DCE</td>
<td>−78 °C</td>
<td>1 h</td>
<td>59%</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>DCE</td>
<td>0 °C</td>
<td>2 h</td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>DCE</td>
<td>rt</td>
<td>1 h</td>
<td>73%</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>DCE</td>
<td>0 °C</td>
<td>1.5 h</td>
<td>72%</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>DCE</td>
<td>rt</td>
<td>2.5 h</td>
<td>69%</td>
</tr>
</tbody>
</table>

*Alkyne 2a was prepared in situ following the conditions shown in Scheme 1.

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Scheme 2. Functionalization of Aryl(dimethyl)aluminum Intermediates

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The aryl(dimethyl)aluminum intermediates were prepared according to the optimized conditions, using Me2AlCl.
terminal alkynes can be employed. Hence, trimethylsilylacetylene 1b and 1-hexyne 1c reacted with pyrones 3a, 3g, and 3k, affording aromatic compounds 15–19 (entries 12–16). Finally, 1-ethynylcyclohexene 1d was also employed, giving 20 in moderate yield (entry 17).

The role played by the Al-group in promoting the reaction together with the consistent meta-substitution pattern observed in products generated by this process provided circumstantial evidence for the operation of a directed cycloaddition process (along the lines depicted in Figure 1). In order to gather further evidence however, we attempted to identify and characterize an intermediate arylaluminum cycloadduct. Although we found these intermediates to be hydrolytically unstable, careful concentration of the reaction mixture derived from the dimethylaluminum promoted cycloaddition of 1c and 3k allowed us to record a $^1$H NMR spectrum of the crude material (Figure 2a). We were able to identify a signal at 0.09 ppm that was consistent with the Me-Al group.8 Furthermore, quenching this reaction mixture with D$_2$O resulted in the formation of compound d-19 after workup (Figure 2b). The $^1$H NMR spectrum shows approximately 90% incorporation of the deuterium label occurred in this case (Figure 2c).8

**Table 2. Scope of the Cycloaddition**

| entry | $R^1$ | $R^2$ | product 4-19 | isolated yield of 4-19 | entry | $R^1$ | $R^2$ | product 4-19 | isolated yield of 4-19 |
|-------|-------|-------|--------------|-----------------------|-------|-------|--------------|-----------------------|
| 1     | Ph (1a) | X = O | X = O (3a) | 78% (4)               | 10    | Ph (1a) | X = S | X = S (3j) | 70% (13)               |
| 2     | Ph (1a) | X = S | X = S (3b) | 0% (5)                | 11    | TMS (1b) | X = NMe (3k)| X = NMe; 69% (14) |
| 3     | Ph (1a) | X = O | X = S (3c) | 76% (7)               | 12    | TMS (1b) | X = NMe (3g)| 80% (15)               |
| 4     | Ph (1a) | X = O | X = NMe2 (3d) | 72% (8) | 13    | TMS (1b) | X = NMe (3f) | 41% (16)               |
| 5     | Ph (1a) | X = O | X = NMe2 (3e) | 72% (8) | 14    | Bu' (1c) | X = NMe (3a) | 73% (17)               |
| 6     | Ph (1a) | X = O | X = NMe2 (3f) | 67% (9) | 15    | Bu' (1c) | X = NMe (3g) | 72% (18)               |
| 7     | Ph (1a) | X = O | X = NMe2 (3g) | 78% (10) | 16    | Bu' (1c) | X = NMe (3k) | 82% (19)               |
| 8     | Ph (1a) | X = O | X = S (3h) | 0% (11)               | 17    | 1-Cyclohexenyl (1d) | X = O; 0% (11) | 55% (20)               |
| 9     | Ph (1a) | X = S | X = S (3i) | 0% (12)               |       |       |       |           |                        |

*Alkyne (1a–d) (3 equiv), BuLi (3 equiv), Et$_2$AlCl (3 equiv); pyrone (3a–k) (1 equiv), rt, 1 h. $^b$Pyrone substrate was recovered. $^c$Reaction conducted for 3 h. $^d$Reaction conducted for 12 h.

(8) Although we have been unable to gather clear evidence for the formation of a Lewis acid-base complex in these products (e.g. B in Figure 2) Blum and co-workers have reported similar intramolecularly stabilized dialkyl(aryl)aluminum complexes; see: Blum, J.; Gelman, D.; Baidossi, W.; Sharkh, E.; Rosenfeld, A.; Aizenshtat, Z. J. Org. Chem. 1997, 62, 8681.
Finally, we wanted to investigate the synthetic potential of the aryl(dimethyl)aluminum intermediates, and some illustrative examples are shown in Scheme 2. First, we found that the intermediate arylaluminum compounds reacted smoothly with iodine, affording iodobenzene derivatives 21 and 22 in high yield. Moreover, when the intermediate was treated with boron trichloride, dimethylboryl product 23 was obtained in 74% yield. The latter could be transformed into methylketone 24 upon exposure to methyl lithium; a similar transformation could be accomplished directly from the intermediate aluminum species to afford methylketone 25 in 84% yield. Overall, this technique complements our recent cycloaddition chemistry of alkynyldifluoroboranes, as it offers a one-pot benzannulation of terminal alkynes, with the option of generating arylhalides or boranes depending on the work-up employed.

In conclusion, we have demonstrated that in situ generated alkynylaluminum reagents undergo rapid cycloaddition reactions with 2-pyrones bearing proximal Lewis bases. This method provides an effective route to functionalized benzene derivatives with predictable substitution patterns and complete regiocontrol.

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Supporting Information Available. Full experimental details for the syntheses reported are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.