Coupling of \(\alpha,\alpha\)-difluoro-substituted organozinc reagents with 1-bromoalkynes

Artem A. Zemtsov\(^1\), Alexander D. Volodin\(^1,2\), Vitalij V. Levin\(^1\), Marina I. Struchkova\(^1\) and Alexander D. Dilman\(^*1\)

Abstract

\(\alpha,\alpha\)-Difluoro-substituted organozinc reagents generated from conventional organozinc compounds and difluorocarbene couple with 1-bromoalkynes affording gem-difluorinated alkynes. The cross-coupling proceeds in the presence of catalytic amounts of copper iodide in dimethylformamide under ligand-free conditions.

Introduction

\(\text{gem-Difluorinated organic compounds have attracted increasing attention nowadays due to their applicability in medicinal chemistry [1,2] and other fields. Indeed, unique stereoelectronic properties of the CF}_2\text{-unit may be exploited in conformational analysis [3-5], carbohydrate and peptide research [6,7], and reaction engineering [8,9].}

Typically, the difluoromethylene fragment is created by deoxyfluorination, which requires harsh or hazardous conditions [10,11]. Alternatively, functional group manipulations starting from available CF\(_2\)-containing building blocks can be considered, but multistep sequences render this approach laborious [12-14]. Difluoro-substituted cyclopropanes and cyclopropenes constitute a specific class of compounds accessible by difluorocarbene addition to multiple bonds [15].

Recently, we proposed a general method for assembling \(\text{gem-difluorinated structures from organozinc reagents I, difluorocarbene, and a terminating electrophile [16-21] (Scheme 1). (Bromodifluoromethyl)trimethylsilane [16-18] or potassium bromodifluoroacetate [19] can be used as precursors of difluorocarbene. In this process, the use of C-electrophiles is particularly important since it allows for the formation of two C–C bonds within one experimental run. Previously, as C-elec-
trophiles in this methodology, only allylic substrates [17] and nitrostryrenes (with the NO₂ serving as a leaving group) [20], were employed. Herein, we report that 1-bromoalkynes, which are known to be involved in reactions with various organometallic compounds [22-27], can be used as suitable coupling partners for difluorinated organozinc compounds 2. This reaction provides straightforward access to α,α-difluorinated alkynes [13,14,28-31]. Our method is based on facile zinc/copper exchange allowing for versatile couplings described for non-fluorinated organozinc compounds [32-37].

Results and Discussion

Organozinc compound 2a generated from benzylzinc bromide was first evaluated in a reaction with haloalkynes derived from phenylacetylene (Table 1). First, most reactive iodo-substituted alkyne 3a-I (X = I) was evaluated in the presence of copper iodide (10 mol %). Expected product 4a was formed in 12% yield, but its yield was tripled simply by adding 2 equiv of DMF additive (Table 1, entries 1 and 2). However, in these experiments, the reaction mixtures contained about 40% of (2,2-difluoro-2-iodoethyl)benzene (PhCH₂CF₂I) arising from zinc/iodine exchange between 2a and the iodoalkyne. Chloroalkyne 3a-Cl was markedly less reactive, likely because of the strong carbon–chlorine bond. Fortunately, bromoalkyne 3a-Br provided the best results, with the optimal conditions involving the use of DMF as a solvent and only 5 mol % of copper iodide at 0 °C to room temperature, which afforded the coupling product in 79% isolated yield (Table 1, entry 5). The addition of various ligands, as well as the use of other copper salts, did not have a beneficial effect.

Under the optimized conditions, a series of organozinc compounds 2 were coupled with bromoalkynes 3 (Table 2). Good yields of coupling products 4 were typically achieved. The reaction tolerates ester groups or TBS-protected hydroxy groups. Aromatic iodide also remains unaffected (Table 2, entry 2).

As for the mechanism, we believe that the reaction starts with the zinc/copper exchange resulting in the formation of fluorinated organocopper species 5 (Scheme 2). Compound 5 inter-

Table 1: Optimization studies.

| Entry | X     | 2a (equiv) | Conditions          | Solvent | Cul (equiv) | Additive (equiv) | Yield of 4a, %<sup>a</sup> |
|-------|-------|------------|---------------------|---------|-------------|-------------------|----------------------------|
| 1     | I     | 2          | -50 °C → rt; 4 h at rt | MeCN    | 0.1         | -                 | 12                        |
| 2     | I     | 1.3        | -50 °C → rt; 4 h at rt | MeCN    | 0.1         | DMF (2)           | 35                        |
| 3     | Cl    | 2          | 0 °C → rt; 16 h at rt | MeCN    | 0.1         | DMF (2)           | 32                        |
| 4     | Br    | 1.5        | 0 °C → rt; 16 h at rt | MeCN    | 0.1         | DMF (2)           | 60                        |
| 5     | Br    | 1.5        | 0 °C → rt; 16 h at rt | DMF     | 0.05        | -                 | 79<sup>b</sup>            |

<sup>a</sup>Determined by <sup>19</sup>F NMR with internal standard. <sup>b</sup>Isolated yield.
Table 2: Reaction of organozinc compounds 2 with bromoalkynes 3.

| Entry | 2 | 3 | 4 | Yield of 4, %<sup>a</sup> |
|-------|---|---|---|--------------------------|
| 1     | PhZnBr<sub>2a</sub> | Br<sub>3</sub>CO<sub>2</sub>Me<sub>2b</sub> | Ph<sub>4b</sub> | 84 |
| 2     | 2a | 3c | Ph<sub>4c</sub> | 82 |
| 3     | 2a | Br<sub>3</sub>F<sub>3d</sub> | Ph<sub>4d</sub> | 70 |
| 4     | 2a | Br<sub>3</sub>CO<sub>2</sub>Et<sub>3e</sub> | Ph<sub>4e</sub> | 84 |
| 5     | 2a | Br<sub>3</sub>OBz<sub>3f</sub> | Ph<sub>4f</sub> | 67 |
| 6<sup>b</sup> | 2a | Br<sub>3</sub>OTBS<sub>3g</sub> | Ph<sub>4g</sub> | 80 |
| 7<sup>b</sup> | 2a | Br<sub>3</sub>OTBS<sub>3h</sub> | Ph<sub>4h</sub> | 75 |
| 8     | MeO<sub>2</sub>C<sub>2b</sub> | Br<sub>3</sub>Ph<sub>3a-Br</sub> | MeO<sub>2</sub>C<sub>4i</sub> | 80 |
| 9     | EtO<sub>2e</sub> | Br<sub>3</sub>Ph<sub>3a-Br</sub> | EtO<sub>4j</sub> | 81 |
acts with bromoalkyne 3 either by oxidative addition generating copper(III) intermediate 6 or by triple bond carbometallation [38] generating copper(I) intermediate 7. Subsequent reductive elimination (from 6) or β-elimination (from 7) leads to the product and regenerates the copper(I) catalyst.

**Scheme 2**: Proposed mechanism.

**Conclusion**

In summary, a method for the copper-catalyzed coupling of α,α-difluoro-substituted organozinc compounds with 1-bromoalkynes has been developed. The reaction is performed under mild conditions affording gem-difluoro-substituted alkynes in good yields.
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