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Zirconium-catalyzed methylalumination of heterosubstituted arylethynes: Factors affecting the regio-, stereo-, and chemoselectivities

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Dedicated to Professor Gerhard Erker on the occasion of his 60th birthday.

Abstract

The Zr-catalyzed methylalumination of heterosubstituted arylethynes containing O, S, Cl, and Si can proceed in high yields (>70%) and in a highly regio- and stereoselective manner ($\geqslant$98–99%), although SO_2Ph, Br, and Cl in a benzylic position present serious chemoselectivity-related problems. The low regioselectivity of 60% initially observed with *o*-ethynylphenol (**1a**) has been elevated to $\geqslant$98% through the use of either a catalytic amount of $Zr(ebi)Cl_2$ or $Zr(2\text{-Me-Ind})_2Cl_2$ or, more conveniently, the stoichiometric amount of $ZrCp_2Cl_2$, $ZrCp_2MeCl$, or $ZrCp_2Me_2$ in conjunction with the use of a deficient amount (0.9 molar equiv.) of I_2 for subsequent iodinolysis.

Keywords: Methylalumination with Me_3Al; Heterosubstituted arylethynes; (*E*)-1-iodo-2-arylpropenes; $ZrCp_2Cl_2$ and its derivatives; Regio- and stereoselectivities

1. Introduction

The Zr-catalyzed carboalumination, especially methylalumination, of terminal alkynes reported first by the authors' group in 1978 [1] has since been developed into a preferred method for the synthesis of methyl-substituted (*E*)-trisubstituted alkenes representing a wide variety of natural products and related compounds of biological and medicinal importance. A recent survey indicates that well over 100 complex natural products have been synthesized by using this reaction in one or more crucial steps [2]. In the absence of any heterofunctional groups in the alkyne substrates, this reaction is highly stereoselective ($\geqslant$98–99% *syn* addition), regioselective (generally ca. 95%), and dependably and widely applicable. Furthermore, the regioselectivity can be improved to $\geqslant$98–99% through the use of bulky derivatives of $ZrCp_2Cl_2$, such as, $Zr(ebi)Cl_2$, where ebi is ethylenebis(indenyl), as recently reported by Lipshutz [3]. Alternatively, high regioselectivity levels ($\geqslant$98–99%) can also be attained through the use of a controlled amount of electrophile, such as I_2, for derivatization of methylalumination products, since the desired terminally aluminated products, in general, are considerably more reactive than the internally aluminated byproducts, presumably because of greater steric hindrance around the alkenylcarbon–Al bond in the latter [4].

The presence of one or more heterofunctional groups in the terminal alkynes can exert significant influences on selectivity. In terms of chemoselectivity, most of the carbonyl groups can be competitively reduced, and it is therefore advisable to introduce them later. Fortunately, halogens including Cl, Br, and I are accommodated except perhaps in the allylic, propargylic, benzylic, and other similarly activated positions, a particularly noteworthy example of this class being the preparation of (*E*)-1,4-diiodo-2-methyl-1-butene from 4-iodo-1-butyne [5]. Perhaps more importantly, hydroxyl groups can be accommodated widely even in the propargylic position, provided that free unprotected alcohols are used in conjunction with one

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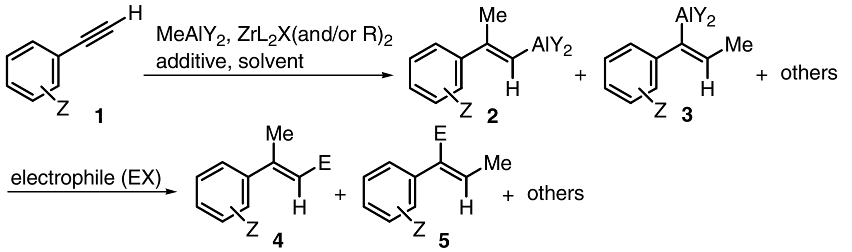

X: Cl, Br, or I. R = Me, etc. Y: Me, Cl. Z: OH, Cl, OMe, CH_2OH, CH_2SPh, CH_2SiMe_3, etc. EX = I_2, NBS, etc.
L: Cp = η^5-C_5H_5, Cp* = η^5-C_5Me_5, Ind = Indenyl, 2-Me-Ind = 2-methylindenyl, ebi = ethylenebis(indenyl)

Scheme 1.

additional equivalent of Me_3Al for in situ generation of aluminum alkoxides [5]. Although, remote OH groups protected with silyl, benzyl, and other groups may be better tolerated, their presence in the propargylic, homopropargylic and other related positions can be problematic, even though the ^{i}Pr$_3$Si (TIPS) group may be tolerated [3]. With these precautions, hydroxyl-containing 1-alkynes including various hydroxyl-substituted enynes have indeed been employed in highly stereo- and regioselective manners [2].

In conjunction with application of the Zr-catalyzed methylalumination to the synthesis of arylated alkene-containing natural products, we recently ran the Zr-catalyzed methylalumination of *o*-ethynylphenol (**1a**) with Me_3Al (3 molar equiv.) and $ZrCp_2Cl_2$ (5 mol%), and observed an unexpectedly low regioselectivity of about 60%, as detailed below. We then noted that, even though phenylethyne was one of the first substrates used in this reaction [1a], little has since been investigated on the use of its heterosubstituted derivatives. Below, we describe the results of our investigation of the Zr-mediated methylalumination of heterofunctionalized arylethynes, which has, in fact, proceeded, in most cases, normally and satisfactorily. Since some of the reactions of *o*-substituted phenylethynes were sluggish, one molar equivalent of H_2O and one additional equivalent of Me_3Al were used to in situ generate methylaluminoxane, leading to acceleration of the reaction, as originally devised by Wipf [6] (see Scheme 1).

2. Results and discussion

The results summarized in Table 1 indicate the following:

(1) All except the $PhSO_2$-containing **1h** (Entry 8) undergo the Zr-catalyzed methylalumination in high yields (72–93%).
(2) With halobenzylethynes (**1i** and **1j**), methylation of benzyl halides takes place concurrently to produce **6** (Entries 9 and 10). These benzylic halogens must therefore be introduced later via halogenation of **4f**, for example.
(3) It is noteworthy that both phenolic and benzylic OH groups can be readily accommodated without protection (Entries 1, 3, 4, and 6).
(4) In the case of **1a** containing an OH group in the ortho position, however, a drastically lower regioselectivity of 60% for the expected major product, i.e., β-**4a**, was observed. Fortunately, this problem has been solved through modification of the methylalumination procedure, as discussed later.
(5) Despite the fact that the internally metalated α isomer of the product contains a benzylic metal, which is normally strongly favored, the high regioselectivity level of the ⩾93% favoring the β isomer has been observed except in the case of **1a**. In particular, the *β*/*α* ratios observed for the iodinolysis products **4** were ⩾98–99% with no indication of the presence of the α isomer at the detection level of S/N ratios of ⩾50–100, except in the cases of **1a**, **1b**, and **1c** (Entries 1–3). In the cases of **1b** and **1c**, however, the use of 0.9 molar equiv. of I_2 led to the *β*/*α* ratio of 99/1, even though the products yields were necessarily lower (80% for **4b** and 81% for **4c**).
(6) In all cases where the Zr-catalyzed methylalumination proceeded, a uniformly high stereoselectivity level of ⩾98–99% by ^{13}C NMR spectroscopy has been observed. Attempt to induce synthetically useful, clean stereoisomerization similar to that observed with 3-methyl-4-alumino-3-buten-1-ol [7] has thus far been unsuccessful. Despite some difficulties, observed with **1a**, **1h**, **1i**, and **1j**, it is gratifying to find that, in all of the other seven cases studied, the Zr-catalyzed methylalumination of arylethynes (**1**) that are arylically and benzylically substituted with heterofunctional groups containing O, S, Cl, and Si proceeds satisfactorily as detailed above and summarized in Table 1.

The uniquely lower regioselectivity of 60% observed with **1a** was then dealt with. In this case, the formation of metal-containing five-membered species (**7**) was thought to be favorable and critical. If so, the corresponding formation of six-membered species (**8**) must be comparatively insignificant, as judged by the results observed with **1f** (Entry 6 in Table 1). Rather than probing structural and mechanistic details, we opted for varying some of the readily changeable reaction parameters, which led to the experimental results that are summarized in Table 2.