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AlCl₃-Promoted Facile *E*-to-*Z* Isomerization Route to (*Z*)-2-Methyl-1-buten-1,4-ylidene Synthons for Highly Efficient and Selective (*Z*)-Isoprenoid Synthesis

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Dedicated to Professor Alain Krief in great appreciation of his life-long contributions to organic synthesis

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Abstract

Zr-catalyzed methylalumination of 3-buten-1-ols followed by AlCl₃-promoted stereoisomerization at 50 °C for 6 h provides 4-iodo-3-methyl-3-buten-1-ols **2b** and **6** of 98 *Z* configuration in 87 and 67% yields, respectively. (*Z*)-1,4-Diiodo-2-methyl-1-butene (**1b**) obtainable by iodination of **2b** is a valuable synthon for efficient and selective syntheses of (*Z*)-alkene containing isoprenoids.

Keywords

Carboalumination; Zirconium; Isomerization; Stereoselectivity; Terpenoid

Introduction

Stereo- and regioselective synthesis of 1,5-dienes and oligoenes thereof representing various terpenoidal natural products had provided a major synthetic challenge until the development of the Pd-catalyzed homoallyl(or homopropargyl)–alkenyl coupling route first reported in 1980.^[1] In sharp contrast with the intrinsically capricious allyl–allyl coupling route requiring typically several steps for the formation of just one critical C—C bond linking two allylic moieties,^[2] the Pd-catalyzed cross-coupling reaction of alkenyl iodides with either homopropargylzinc or homoallylzinc reagents reliably proceeds in high yields with strict (98%) control of regio- and stereochemical identities with little or no sign of β-elimination.^[1,3–5] Particularly attractive is the two-step preparation of (*E*)-1,4-diiodo-2-methyl-1-butene (**1a**)^[3a] of 98% *E* configuration (Scheme 1) from homopropargyl alcohol via Zr-catalyzed methylalumination, ZMA hereafter, permitting one-pot homologation of (all-*E*)-isoprenoid skeletons by one “one isoprene equivalent” that has been applied to highly efficient and selective syntheses of coenzyme Q_n (*n* = 3 and 10) and menaquinone-3.^[3a] For the synthesis of (*Z*)-trisubstituted alkene-containing isoprenoids, (*Z*)-1,4-diiodo-2-methyl-1-butene (**1b**) of 98% stereoisomeric purity was prepared by refluxing the reaction mixture containing the *E*-isomer in (CH₂Cl)₂ for 3–5 days (Scheme 1),^[6] and it has also been successfully used for the synthesis of (*Z*)-trisubstituted alkene-containing farnesols and (2*E*, 6*Z*, 10*E*)-geranylgeraniol.^[3a] As attractive as it is, the rather harsh conditions for isomerization pointed to the obvious need for improvement.

Herein we report our recent findings that have led to a remarkably mild and highly satisfactory procedure for the preparation of **1b** of 98% stereoisomeric purity in 75% yield in 2 steps from 3-butyne-1-ol, thereby making the ZMA–Pd-catalyzed alkenylation–homoallylation tandem protocol highly satisfactory not only for the synthesis of (all-*E*)-isoprenoids but also for (*Z*)-trisubstituted alkene-containing isomers as well.

Results and Discussion

In the hope of promoting the sluggish stereoisomerization mentioned above, Lewis acid-promoted stereoisomerization was considered. Although both organoalanes and ZrCp_2Cl_2 used for ZMA reaction are considered to be Lewis acidic, more effective Lewis acids were evidently needed. We therefore chose and added to the completed ZMA reaction mixture methylaluminoxane (MAO) used for promoting the Zr–Al-cocatalyzed Kaminsky modification of the Ziegler–Natta alkene polymerization,^[7] AlCl_3 , MeAlCl_2 , Me_2AlCl , as well as $\text{BF}_3\cdot\text{OEt}_2$ and InCl_3 . The results summarized in Table 1 indicate the following.

1. AlCl_3 and MAO are both effective in accelerating the desired *E*- to *Z*-isomerization, but AlCl_3 is the promoter of choice (Entries 3 and 7).
2. It appears mandatory to use more than 1 molar equivalent of AlCl_3 (Entries 5–7) at moderately elevated temperature, e.g., 50 °C (Entries 4 and 7).
3. Under the conditions employed, MeAlCl_2 , Me_2AlCl , $\text{BF}_3\cdot\text{OEt}_2$ and InCl_3 are not effective (Entries 8–11).

Although mechanistic details of the AlCl_3 -promoted stereoisomerization remain to be further clarified, it is not unreasonable to envision the reaction in terms of a polar cyclization process shown in Scheme 2, which is consistent with (i) the high efficiency of Al–Cl bonded species that are expected to undergo kinetically facile $\text{O}=\text{Cl}$ ligand exchange and [1, 3] Cl migration owing to the presence of 3 lone pairs of electrons as opposed to none for Me group and (ii) formation of the thermodynamically more favorable double Cl-bridged alane dimers as opposed to Me-bridged alane dimers. If this latter item (ii) is indeed a significant factor, the observed isomerization may well be stoichiometric in chloroalanes.

Since our efforts have been focused on the improvement of the synthesis of the single most important (*Z*)-isoprene equivalent (**1b**) obtainable via **2b**, relatively little efforts have thus far been made to explore the scope of the AlCl_3 -promoted stereoisomerization of alkenylalanes that has just been developed. Nonetheless, some preliminary results described below do provide indications of its scope and limitations. 1-Alkynes lacking proximal OH or any heterofunctional group, e.g., 1-octyne, are known to undergo the ZMA reaction,^[8] but such alkenylalane products show no sign of stereoisomerization upon heating them to 50 °C in the presence of AlCl_3 (2.0 equiv). As has long been known,^[9] treatment of propargyl alcohol with Me_3Al (2.5 equiv) and ZrCp_2Cl_2 (0.2 equiv) in $(\text{CH}_2\text{Cl})_2$ at 23 °C for 4 h followed by iodinolysis produced (*E*)-3-iodo-2-methyl-2-propen-1-ol (98% *E*) in 57% yield. When the ZMA reaction mixture was treated with anhydrous AlCl_3 (2.0 equiv) at 50 °C for 6 h and then subjected to iodinolysis, however, (*Z*)-3-iodo-2-methyl-2-propen-1-ol (**3**) of 98% *Z* geometry was obtained albeit in only 33% yield. It should be reminded that **3** can be readily and selectively prepared in higher yield by treating propargyl alcohol with MeMgBr in the presence of a catalytic amount of CuI followed by iodinolysis.^[10]

As previously reported, 2-methyl-3-butyne-1-ol (**4**) and 4-pentyne-2-ol (**5**) can be converted to the expected iodinated alcohols **6** and **7** of 98% *Z* configuration in 61 and 50% yields, respectively, but the isomerization step required refluxing the ZMA product-containing mixtures for 3–5 days.^[3a, 6] Under the AlCl_3 -promoted conditions (heating at 50 °C for 6 h in the presence of 2 equivalents of AlCl_3), **6** (98% *Z*) was obtained in 67% yield. To our

disappointment, however, our attempts to prepare **7** under the same conditions as described above led to extensive decomposition of the ZMA product from **5**. The case of 4-pentyn-1-ol (**8**) is not clean but interesting and promising. As summarized at the bottom of Scheme 3, application of the standard ZMA and AlCl_3 -promoted isomerization protocol reported herein gave a roughly 40/60 mixture of the *Z* and *E* isomers of **9** in 84% combined yield, when the ZMA reaction product was heated to 50 °C for 6 h in the presence of two equivalents of AlCl_3 . After prolonged heating at 50 °C for a total of 48 hours, the *Z/E* ratio was improved to 80/20, but the yield of **9** decreased to 71%. When the ZMA product mixture was refluxed in the presence of AlCl_3 (2 equiv), however, most of the alkenylalane products were decomposed. Chromatographic purification of the 80/20 mixture of the *Z* and *E* isomers of **9** gave 98% pure (*Z*)-**9** in 52% yield. Further improvement is clearly desirable.

Conclusions

1. Zr-catalyzed methylalumination of 3-butyne-1-ol and its 2-methyl derivative (**4**) followed by AlCl_3 -promoted stereoisomerization at 50 °C for 6 h provides 98% *Z* 4-iodo-3-methyl-3-buten-1-ols **2b** and **6** in 87 and 67% yields, respectively. Iodination of **2b** gives (*Z*)-1,4-diiodo-2-methyl-1-butene (**1b**) of 98% isomeric purity in 75% yield from 3-butyne-1-ol. The procedural development reported herein has finally made the Pd-catalyzed homoallyl-alkenyl coupling route to 1,5-diene-containing oligomeric isoprenoids of any geometric combination both highly selective and practically convenient.
2. Although tentative, the available data suggest that a cyclic mechanism requiring an appropriate proximal heterofunctional group, e.g., OH, is operative and that the role of AlCl_3 appears to displace the alkene-bound Me_2Al group with AlCl_2 thereby facilitating configurational inversion via facile polar cyclization.
3. As suggested by the results shown in Scheme 3, the ZMA- AlCl_3 -promoted isomerization process herein reported appears to be applicable to various other types of proximally heterofunctional trisubstituted (*Z*)-alkenyl derivatives containing Al, I and other functional groups, which may, in turn, be further converted to a wide variety of compounds including heterocycles, and explorations along such directions are in progress.

Experimental Section

General

All reactions were carried out under Argon atmosphere. *AlMe₃ is highly pyrophoric!* Reactions were monitored by TLC and GC analysis of reaction aliquots. GC analysis was performed on an HP6890 Gas Chromatograph using an HP-5 capillary column (30 m × 0.32 mm, 0.5 μm film) packed with SE-30 on Chromosorb W. Column chromatography was carried out on 230-400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on a Varian-Inova-300 spectrometer. IR spectra were recorded on a Perkin-Elmer Spectrum 2000 FT-IR spectrometer. LRMS and HRMS were obtained on Hewlett Packed 5995 GC-MS and Finnigan MATL95 mass spectrometers, respectively.

Preparation of (*Z*)-4-Iodo-3-methyl-3-buten-1-ol (**2b**). Representative Procedure for AlCl_3 -Promoted *E*-to-*Z* Isomerization

To a solution of ZrCp_2Cl_2 (0.29 g, 1.0 mmol) in $(\text{CH}_2\text{Cl})_2$ (20 mL) were sequentially added AlMe_3 (1.2 mL, neat, 12.5 mmol) and 3-butyne-1-ol (0.35 g, 5.0 mmol) at 0 °C. The resultant mixture was stirred at 23 °C for 4 h for completion of methylalumination. Anhydrous AlCl_3 powder (1.35 g, 10 mmol) was added to the above reaction mixture in one portion. After

stirring at 50 °C for 6 h, the reaction mixture was quenched with a solution of I₂ (2.54 g, 10 mmol) in THF (20 mL) at –78 °C. The resultant mixture was stirred at –78 °C for 30 min, and then poured into ice-water, extracted with ether, washed with brine, dried over MgSO₄, filtered, and concentrated. Flash chromatography (silica gel, 30% EtOAc in hexanes) afforded (Z)-4-iodo-3-methyl-3-buten-1-ol (**2b**) (0.92 g, 87%, 98% Z) as a liquid: ¹H NMR (300 MHz, CDCl₃) δ 1.89 (d, *J* = 1.2 Hz, 3 H), 2.46 (t, *J* = 6.9 Hz, 2 H), 2.84 (s, 1 H), 3.69 (t, *J* = 6.9 Hz, 2 H), 5.93 (q, *J* = 1.2 Hz, 1 H); ¹³C NMR (75.4 MHz, CDCl₃) δ 23.81, 41.48, 59.80, 76.19, 144.25; IR (neat) 3292, 1580 cm^{–1}; HRMS (CI) *m/z* for M⁺ 211.9696, calcd. 211.9700.

It is also practical to use commercially available AlMe₃ in hexanes. The Zr-catalyzed carboalumination of 3-butyne-1-ol with 2*M* AlMe₃ in hexanes under otherwise the same conditions as described above was complete in 5 h. The subsequent isomerization with AlCl₃ at 50 °C was somewhat slower requiring 18 h for 98% stereoisomerization in 82% yield.

Preparation of (Z)-1, 4-Diiodo-2-methyl-1-butene (1b)

Treatment of (Z)-4-iodo-3-methyl-3-buten-1-ol with PPh₃, I₂, and imidazole in CH₂Cl₂ as previously reported^[3a, 6] afforded the title compound in 86% yield with 98% stereoisomeric purity: ¹H NMR (300 MHz, CDCl₃) δ 1.85 (s, 3 H), 2.82 (t, *J* = 7.6 Hz, 2 H), 3.20 (t, *J* = 7.3 Hz, 2 H), 6.07 (s, 1 H); ¹³C NMR (75.4 MHz, CDCl₃) δ 0.41, 23.00, 42.41, 77.02, 145.70.

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Scheme 1.

Zr-catalyzed carboalumination–double-iodination routes to (*E*)- or (*Z*)-1, 4-diiodo-2-methyl-1-butene (Summary of the previous results)

Scheme 2. Mechanistic hypothesis for AlX_3 -promoted stereoisomerization

Scheme 3.

Application of the ZMA– AlCl_3 -promoted isomerization protocol to other proximally OH-substituted 1-alkynes

Table 1

Lewis acid-promoted stereoisomerization of the ZMA reaction mixture obtained from 3-butyn-1-ol

Entry	Additive (quantity)	Temp. ($^\circ\text{C}$)	Time (h)	2a + 2b (%)	2b/2a
1 ^[a]	none	–	0	91	2/98
2 ^[a]	none	reflux	72	60	98/2
3 ^[b]	MAO (3 equiv)	reflux	24	61	98/2
4	AlCl_3 (2 equiv)	–5	12	72	2/98
5	AlCl_3 (0.25 equiv)	50	12	82	1/50
6	AlCl_3 (1.1 equiv)	50	6	89	3/1
7	AlCl_3 (2 equiv)	50	6	87	98/2
8	MeAlCl_2 (2 equiv)	50	6	88	1/4
9	Me_2AlCl (2 equiv)	50	6	86	1/45
10	InCl_3 (2 equiv)	50	12	70	1/4
11	$\text{BF}_3\cdot\text{OEt}_2$	23	12	[c]	[c]

^[a] Previously reported data.^[6]^[b] Observed by Dr. Z. Tan.^[c] Complex product mixture obtained.