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Selective Preparation of Benzyltitanium Compounds by the Metalative Reppe Reaction. Its Application to the First Synthesis of Alcyopterosin A

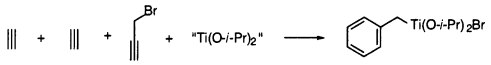
Ryoichi Tanaka,† Yoshitaka Nakano,† Daisuke Suzuki,‡,§ Hirokazu Urabe,† and Fumie Sato*,‡

Departments of Biological Information and Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

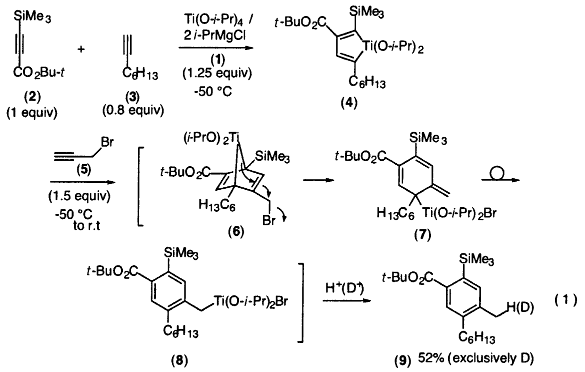
Received May 22, 2002

Benzylmetal compounds occupy an important position among organometallic compounds that allow the introduction of an aromatic moiety into organic molecules.[1] While the preparation of benzylmetals continues to utilize metalation of appropriate aromatic compounds,[1] a conceptually different method, starting from non-aromatic precursors, could be a useful alternative. Herein we report such a novel transformation based on the metalative Reppe reaction of acetylenes and a titanium(II) reagent, which directly and regioselectively produces benzyltitanium compounds as shown in Scheme 1.[2]

Scheme 1. New Metalative Reppe Reaction Producing Benzyltitanium Compounds



Equation 1 illustrates the actual transformation of Scheme 1.[3] Thus, titanacyclopentadiene **4** was first prepared from two different, unsymmetrical acetylenes, **2** and **3** (as the first and second acetylenes), and a divalent titanium alkoxide, $Ti(O\text{-}i\text{-}Pr)_4$/2 *i*-PrMgCl (**1**),[4] at −50 °C.[5] Propargyl bromide (**5**)[6] was then added as the third acetylene. The reaction mixture was allowed to warm to room temperature to give a single benzyltitanium compound **8**, the presence of which was confirmed by its hydrolysis and deuteriolysis to give **9** as the sole aromatic compound. It should be noted that this method achieved the selective cyclotrimerization of three different, unsymmetrical acetylenes to a single aromatic compound, which has been only scarcely precedented.[2,7] Another synthetic advantage is that the ester group in acetylene **2** survived the reaction conditions to allow the generation of a functionalized benzylmetal species.



A proposed mechanism of this reaction is also drawn in eq 1, where the propargyl bromide is incorporated into the titanacycle **4** in a regioselective manner[8] and, perhaps, in equilibrium to form **6** as a transient species. However, elimination of the leaving group (Br) from this intermediate **6** should make the whole reaction irreversible, to lead to the formation of benzyltitanium compound **8** via the aromatization of **7**.

Other results are summarized in Table 1. The benzyltitanium **8** in eq 1 could be iodinated (with iodine) or oxygenated (with dry oxygen gas under atmospheric pressure) to afford benzyl iodide **10** or alcohol **11**, respectively (entries 3 and 4). Such synthetic applications of the resulting titanium compounds would broaden the utility of this method.[9] Enyne **12** gave the desired aromatic compound **14** after hydrolysis of **13** without any complication (entry 5). Acetylene **15** underwent the cyclotrimerization with **16** and **5** as well to give a mixture of benzyltitanium compounds **17**−**19**, as evidenced by hydrolysis and deuteriolysis (entry 6).[3] Nonetheless, as **17** and **18** have the same structure except for the arylmetal portion (Si or Ti),[10] the regioselectivity regarding the uptake of propargyl bromide ((**17** + **18**)/**19** = 94:6) did prove very high. Hydrolysis of a mixture of **17**−**19**, subsequent desilylation with CF_3CO_2H, and purification on silica gel furnished the major aromatic compound **20** in pure form, as shown in entry 6.[3]

Tethered acetylenes (i.e., diynes) are also feasible substrates in this reaction to give bicyclic compounds (Table 1, entries 7−14). The acetylene−titanium complex generated from acetylenic ester **21** underwent orderly coupling with each of the two acetylenic bonds of diyne **22** to give a single benzyltitanium intermediate **23**, which, upon hydrolysis, gave aromatic ester **24** in good yield (entry 7). The smooth generation of a sterically hindered benzylmetal species such as **23** is an interesting application of this method. Similarly, the cyclotrimerization of acetylenic amide **25** and diyne **26** afforded aromatic amide **28** (entry 8). Alternatively, oxygenation of the intermediate titanium species **30** with O_2 produced a benzyl alcohol, which was then lactonized to give tricyclic phthalide derivative **31** (entry 9). As precedented in entry 6, the assembly of acetylene **15** and diyne **26** afforded a mixture of two benzyltitanium species, **32** and **33** (entry 10), which finally led to a single aromatic compound **34** by the same treatment as described in entry 6. On the other hand, entries 11−14 show that diyne **35** worked as the first and second acetylenes to give benzyltitanium compound **36**, which was subsequently hydrolyzed, iodinated, oxygenated, or alkylated to give the corresponding products **37**−**40** in good yields. It should be noted that the silicon−titanium crossing observed in the aforementioned entries 6 and 10 was not seen at all in this combination of acetylenes.

The convenient preparation of bicyclic aromatic compounds as shown above prompted us to explore the first concise synthesis of

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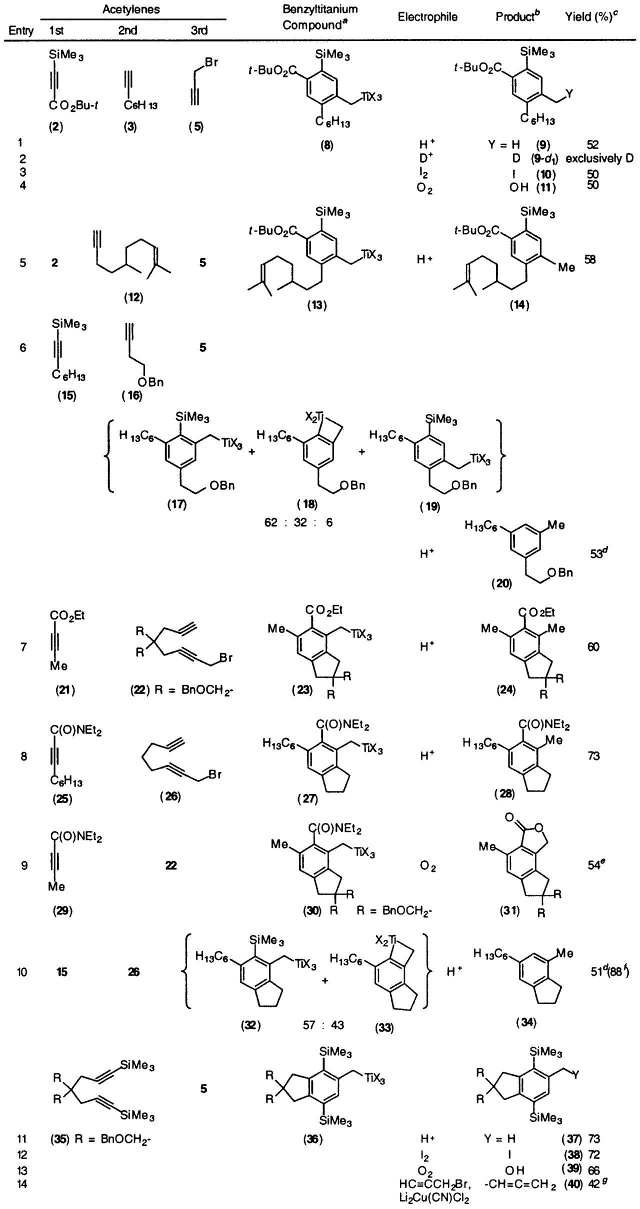
* Corresponding author. E-mail: fsato@bio.titech.ac.jp.
† Department of Biological Information.
‡ Department of Biomolecular Engineering.
§ Research Fellow of the Japan Society for the Promotion of Science.

10.1021/ja027008o CCC: $22.00

Table 1. Preparation of Benzyltitanium Compounds



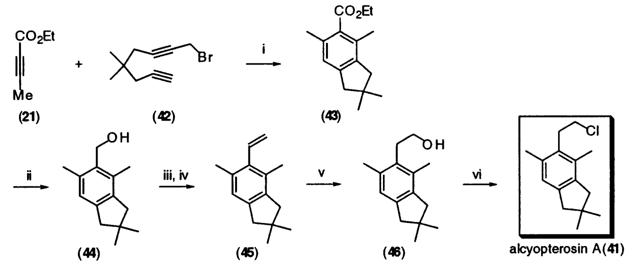
Entry	Acetylenes 1st	Acetylenes 2nd	Acetylenes 3rd	Benzyltitanium Compound[a]	Electrophile	Product[b]	Yield (%)[c]
1	**(2)**	**(3)**	**(5)**	**(8)**	H^+	Y = H **(9)**	52
2					D^+	D **(9-*d*$_1$)**	exclusively D
3					I_2	I **(10)**	50
4					O_2	OH **(11)**	50
5	**2**	**(12)**	**5**	**(13)**	H^+	**(14)**	58
6	**(15)**	**(16)**	**5**	{ **(17)** + **(18)** + **(19)** } 62 : 32 : 6	H^+	**(20)**	53[d]
7	**(21)**	**(22)** R = $BnOCH_2$-		**(23)**	H^+	**(24)**	60
8	**(25)**	**(26)**		**(27)**	H^+	**(28)**	73
9	**(29)**	**22**		**(30)** R = $BnOCH_2$-	O_2	**(31)**	54[e]
10	**15**	**26**		{ **(32)** + **(33)** } 57 : 43	H^+	**(34)**	51[d](88[f])
11	**(35)** R = $BnOCH_2$-		**5**	**(36)**	H^+	Y = H **(37)**	73
12					I_2	I **(38)**	72
13					O_2	OH **(39)**	66
14					$HC{\equiv}CCH_2Br$, $Li_2Cu(CN)Cl_2$	-CH=C=CH$_2$ **(40)**	42[g]

[a] Structure deduced by spectroscopic analysis of the products resulting from hydrolysis, deuteriolysis, and other reactions with electrophiles. TiX_3 is likely $Ti(O\text{-}i\text{-}Pr)_2Br$. [b] No other isomer(s) detected in a crude reaction mixture, unless otherwise stated. [c] Isolated, overall yields from acetylenes. [d] After desilylation with CF_3CO_2H. See text. [e] After lactonization with *p*-$MeC_6H_4SO_3H$. [f] Yield of a purified mixture of protonated **32** and **33** (6:4) before desilylation. [g] Yield not optimized.

alcyopterosin A (**41**) (Scheme 2). Its isolation, characterization, and mild cytotoxicity toward human tumor cell lines were quite recently reported.[11,12] The cyclotrimerization of acetylenic ester **21** and diyne **42** afforded the properly substituted aromatic ring **43** in one step and in 73% yield after hydrolysis. Modification of the ester portion of **43** to an alcohol (**44**), vinyl group (**45**), hydroxyethyl group (**46**), and, finally, the chloroethyl group by standard methods completed the first synthesis of alcyopterosin A (**41**).

In conclusion, a novel preparation of benzyltitanium compounds, which may have a functional group such as ester or amide, from three acetylenes and the titanium alkoxide has been reported. Further extension and application of this method are under active investigation.

Scheme 2. Total Synthesis of Alcyopterosin A[a]



[a] Reagents and conditions: (i) $Ti(O\text{-}i\text{-}Pr)_4$/2 *i*-PrMgCl, then H^+, 73%; (ii) $LiAlH_4$, 91%; (iii) PCC, 96%; (iv) $Ph_3P{=}CH_2$, 86%; (v) $BH_3{\cdot}THF$, then H_2O_2/OH^-, 67%; (vi) $SOCl_2$, LiCl, pyridine, 70%.

Acknowledgment. We thank the Japan Society for the Promotion of Science for financial support.

Supporting Information Available: Experimental procedures, physical properties of products, and a proposed reaction course (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) For the metalative Reppe reaction giving aryltitanium compounds and pertinent references on acetylene cyclotrimerization, see: Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925−7926.

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(6) Propargyl chloride or phosphate gave inferior results to the bromide. Reaction of allyl phenyl ether with diaryloxytitanacyclopentadienes, generating (cyclohexadienylmethyl)titanium species, was reported: (a) Balaich, G. J.; Rothwell, I. P. *Tetrahedron* **1995**, *51*, 4463−4470. Copper-mediated coupling of propargyl bromide with zirconacycles is known, but the formation of benzylmetal reagents has not been evidenced: (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059−5067.

(7) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835−2841.

(8) Rationale of this regioselection so far remains unclear and should await further study. Other possible paths from **4** to **8** are shown in the Supporting Information.

(9) For general synthetic application of organotitanium compounds, see: (a) Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139−172. (b) Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 1994; pp 195−282.

(10) A plausible mechanism of the formation of **18** during the cyclotrimerization and its basis are provided in the Supporting Information.

(11) Palermo, J. A.; Brasco, M. F. R.; Spagnuolo, C.; Seldes, A. M. *J. Org. Chem.* **2000**, *65*, 4482−4486.

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JA027008O