

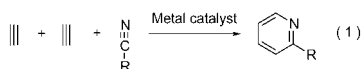
Selective Syntheses of Metalated Pyridines from Two Different Unsymmetrical Acetylenes, a Nitrile, and a Titanium(II) Alkoxide

Daisuke Suzuki,^{†,§} Ryoichi Tanaka,[‡] Hirokazu Urabe,[‡] and Fumie Sato^{*†}

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

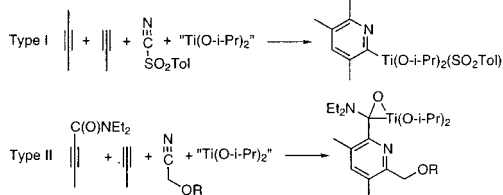
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There is a wide variety of preparative methods of pyridines,¹ among which the Reppe-type assembly of acetylenes and a nitrile as formulated in eq 1 has recently attracted much attention, because

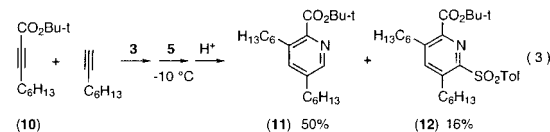
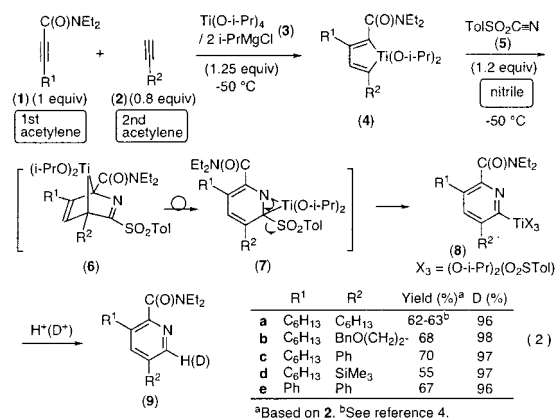


of its straightforward concept, easy availability of starting materials, and synthetic flexibility.² Although many reports along this line have appeared,³ regioselective assembly of two different, unsymmetrical acetylenes and a nitrile, leading to a single pyridine product, still remains unsolved. Herein we report novel types of the selective synthesis of pyridines, which, for the first time, realize this objective and also directly produce metalated pyridines, often a more versatile species than pyridines themselves,^{1c} as shown in types I and II of Scheme 1.

Scheme 1. Formulation of New Syntheses of Metalated Pyridines



In both transformations, the experimental procedures are quite simple and can be carried out in one pot.⁴ Dialkoxytitanacyclopentadienes **4** were first gathered from two different, unsymmetrical acetylenes **1** and **2** (as the first and second acetylenes) and a divalent titanium alkoxide reagent, $\text{Ti}(\text{O}-i\text{-Pr})_4/2$ $i\text{-PrMgCl}$ (**3**),⁵ at -50°C in a highly regioselective manner (eq 2).⁶ Once sulfonylnitrile **5**⁷ was added, the regioselective uptake of the nitrile into the titanacyclopentadiene took place. Hydrolytic workup afforded single pyridines **9**,⁸ and more importantly, deuteriolysis gave the single deuterated counterparts **9-d** with high deuterium incorporation, confirming the generation of pyridyltitanium compounds **8** before aqueous workup (type I in Scheme 1). An informative observation associated with the reaction course of this process has been obtained. Acetylenic ester **10** afforded the expected pyridine **11** as a single isomer (eq 3) similarly to the above reaction, accompanied by a small amount of sulfonylated pyridine **12**.⁹ The latter compound may arise from aerial oxidation of dihydropyridines produced by the hydrolysis of the intermediate titanium complexes such as **6** or **7** in eq 2 before elimination of the sulfonyl group. Thus, the reaction



most likely proceeds as depicted in eq 2 and should resemble the metalative Reppe reaction reported previously.¹⁰

Although this pyridine synthesis starting from 1-(trimethylsilyl)-1-octyne as the first acetylene was unsuccessful, that from dialkylacetylene **13** proved to be viable as shown in eq 4, where the neighboring benzyl ether in the side chain of the titanacycle **14** apparently controls the direction of the incoming nitrile to give pyridine **15** as a single regioisomer.¹¹

The advantageous feature of the formation of titanated pyridines **8** over the conventional metal-catalyzed pyridine synthesis (eq 1) was demonstrated by the subsequent transformations.^{1c,12} Thus, treatment of **8c** with iodine, allyl bromide, or ethylenemalonate (the latter two were under $\text{Li}_2\text{CuCNCl}_2$ catalysis) furnished pyridyl iodide **16** or homologated aromatic compounds **17** and **18** (Figure 1).

Switching nitriles from sulfonyl derivative **5** to alkanenitriles **20** as shown in eq 5 led to another kind of selective pyridine synthesis from two different, unsymmetrical acetylenes (type II in Scheme 1). The addition of α -methoxyacetonitrile (**20a**) to titanacyclopentadiene **19a** followed by aqueous workup produced, to our surprise, pyridinecarbaldehyde **23a** as a single isomer (eq 5).^{8,13} Moreover, deuteriolysis of the same reaction mixture reveals that its aldehyde hydrogen was substituted by deuterium. On the basis of these observations, a plausible reaction course is also shown in eq 5. The regioselective incorporation of the nitrile to the titanacycle **19** produced the intermediate **21**, which aromatized most likely with the concomitant formation of η^2 -carbonyl-titanium complex **22**.¹⁴ This titanium complex was hydrolyzed (or deuterated) to give the

* Address correspondence to this author. E-mail: fsato@bio.titech.ac.jp.

[†] Department of Biomolecular Engineering.

[§] Research Fellow of the Japan Society for the Promotion of Science.

[‡] Department of Biological Information.

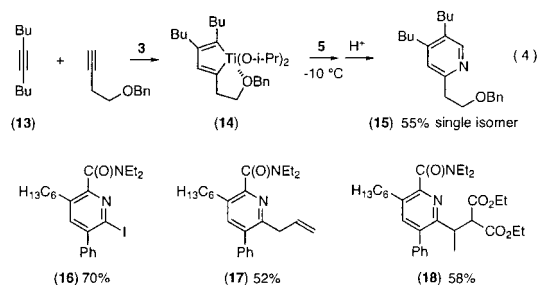
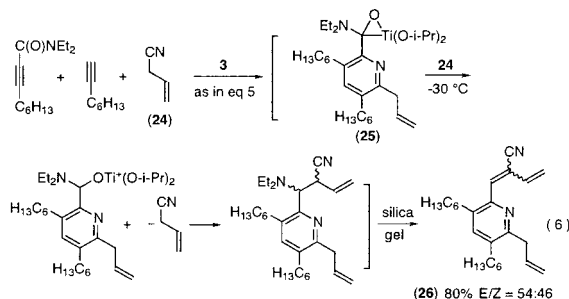
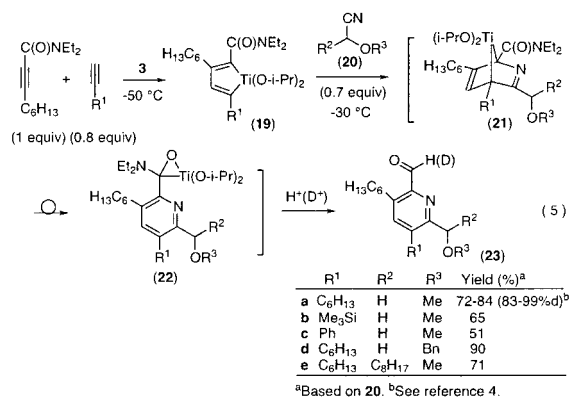


Figure 1. Utility of pyridyltitanium reagent **8c**. Yields are overall from starting acetylenes.

(deuterated) aldehyde **23**. An intriguing utility of the metalated portion of **22** was demonstrated by its reaction with a pronucleophile. When allyl cyanide (**24**, 2 equiv) was used as the nitrile (eq 6), the reaction proceeded beyond the metalated pyridine **25** via the proton transfer from nitrile **24**, giving eventually pyridine **26** as a mixture of separable olefinic stereoisomers.



In conclusion, a combination of two acetylenes, various nitriles, and the titanium alkoxide reagent produced titanated pyridines in a novel way. Particularly, starting this reaction with alkynamide or alkynoate allowed the perfectly regioselective three-component coupling process. Further utility of these metalated heteroaromatic compounds and the mechanistic rationale are under active investigation.

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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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- (7) *p*-Toluenesulfonylnitrile is commercially available and used as such.
- (8) The rationale of this regioselective uptake of nitrile uptake so far remains unclear and should await further study on the structure of intermediates and the reaction mechanism.
- (9) When the reaction was quenched at a lower temperature (–50 °C), sulfonylpyridine **12** became a major constituent (**12** and **11** in **37** and 28% yields, respectively).
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- (13) So far, a simple alkanenitrile such as octanenitrile showed sluggish reaction, suggesting the importance of the presence of a coordinating moiety in the nitrile. Nonetheless, as α -oxynitriles are readily obtained by the cyanohydrin synthesis and its modifications, this reaction will find reasonable application.
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