SYNLETT Spotlight 416

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Hendrickson Reagent
(Triphenylphosphonium Anhydride Trifluoromethane Sulfonate)

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Introduction

The Hendrickson reagent (triphenylphosphonium anhydride trifluoromethane sulfonate) was first reported in 1975.1 It is readily prepared at 0 °C in dichloromethane from triphenylphosphine oxide and trifluoromethanesulfonic anhydride in a 2:1 ratio and used directly as prepared in dichloromethane without the need for isolation.1,2 The Hendrickson reagent is a highly effective and versatile dehydrating reagent due to the strong electron-withdrawing capabilities of the triflyl group and special affinity for oxygen based on the very strong P–O bond.3 It is selective for attack on oxygen without any intrinsic nucleophiles, avoiding formation of unwanted by-products. It has successfully been employed in ester, ether and amide formation as well as in the rapid conversion of aldoximes into nitriles, to yield a variety of alkyl and aryl aldoximes.2–4 These reactions occur in a manner that is analogous to the Mitsunobu reaction, involving an intermediate alkoxyporphonium salt.5,6 The advantages of the Hendrickson reagent over the Mitsunobu reagent are that the recovered triphenylphosphine oxide may be recycled by treatment with trifluoromethanesulfonic anhydride, the use of explosive azodicarboxylates is not required and competing side reactions are avoided.7 Furthermore, a number of methods have recently been reported that can easily overcome, or avoid, the formation and removal of the double-stoichiometric amount of triphenylphosphine oxide, a common problem of phosphine-based dehydrating agents. These methods employ novel derivatives of the Hendrickson reagent such as a copolymer-supported triphenylphosphine ditriflate, an insoluble support allowing for the easy removal of triphenylphosphine or cyclic analogues that can eliminate the step of oxidizing the phosphine into the corresponding oxide prior to trifluoromethylsulfonation.9,10

Abstracts

(A) Xi and co-workers have described a methodology for the efficient synthesis of phenanthridines using the Hendrickson reagent under mild conditions. The method exploits a Hendrickson reagent initiated cascade annulation to achieve a highly reactive imido-carbonium intermediate which undergoes subsequent intramolecular Friedel–Crafts reaction. This method tolerates a wide range of functional groups. Phenanthridines are a core structure of many naturally occurring bioactive alkaloids.11

SYNLETT 2012, 23, 2999–3000
Advanced online publication: 16.11.2012
DOI: 10.1055/s-0032-1317486; Art ID: ST-2012-V0422-V
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(B) Xu and colleagues have reported a flexible protocol involving a two-step strategy to assemble 11H-indolo[3,2-c]quinoline starting from acyclic alkyne substrates. Hendrickson reagent is used as the second step after gold(III)-catalyzed 5-endo-dig cyclisation to promote regioselective 6-endo cyclisation under mild conditions. Naturally occurring alkaloids containing the 11H-indolo[3,2-c]quinoline scaffold have diverse biological properties.12

\[ \text{Reaction (B)} \]

Mossotti and Panza showed that the Hendrickson reagent was able to efficiently perform dehydrative glycosylation of 1-hydroxy-glycosyl donors. The reaction occurs under mild conditions through an anomeric oxophosphonium intermediate detected through nuclear magnetic resonance spectroscopy.15

\[ \text{Reaction (E)} \]

(F) The camptothecin family of alkaloids attracts considerable attention due to their anticancer activities. Zhou et al. showed a total synthesis of camptothecin, in which Hendrickson reagent was used to trigger a mild and efficient cascade reaction that was subsequently followed by a highly enantioselective Sharpless asymmetric (AD) dihydroxylation.16 This method achieved much higher yields than the method previously described by Fortunak, in which trimethylsilyl fluoroborate was used as the activating agent.17

\[ \text{Reaction (F)} \]

References