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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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Janice Irene McCaule was born in Bathurst, New South Wales (NSW), Australia. She graduated in 2007 with a Diploma of Pathology (Laboratory Techniques) from the Sydney Institute of Technical and Further Education NSW before proceeding on to complete a Bachelor of Biotechnology at the University of Wollongong NSW with honours in 2012. Janice is currently studying for a PhD in algal natural product chemistry at the University of Wollongong. Her work on seaweed chemistry also contributes to a screening program underway at the Shoalhaven Marine Freshwater Centre Nowra NSW aimed at identifying Australian seaweed species with desirable functional traits for cultivation in Australia.

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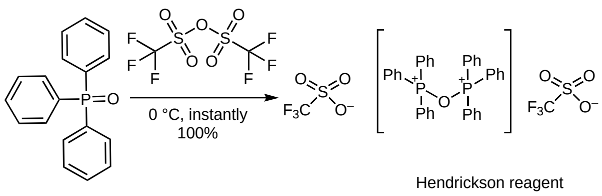
Introduction

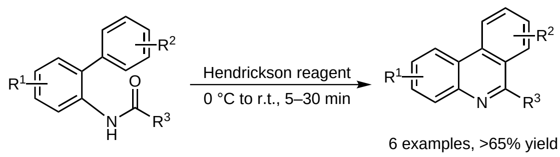
The Hendrickson reagent (triphenylphosphonium anhydride trifluoromethane sulfonate) was first reported in 1975.[1] It is readily prepared at 0 °C in dichloromethane from triphenylphosphine oxide and trifluromethanesulfonic anhydride in a 2:1 ratio and used directly as prepared in dichloromethane without 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 alkoxyphosphonium 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 trifluromethanesulfonic 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[8] or cyclic analogues that can eliminate the step of oxidizing the phosphine into the corresponding oxide prior to trifluoromethylsulfonation.[9,10]



Scheme 1 Preparation of the Hendrickson reagent

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]



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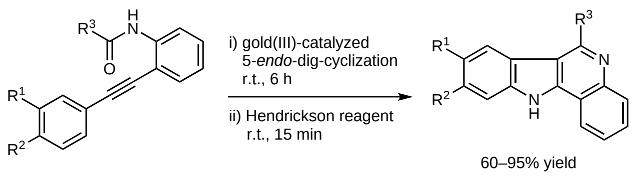
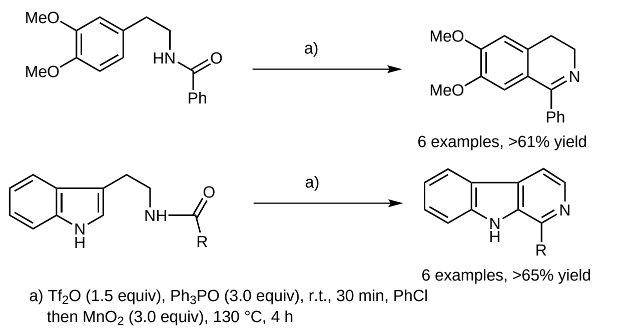
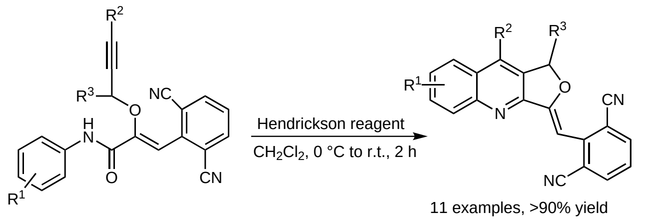
(B) Xu and colleagues have reported a flexible protocol involving a two-step strategy to assemble 11*H*-indolo[3,2-*c*]quinoline starting from acyclic alkyne substrates. Hendrickson reagent is used as the second step after gold(III)-catalyzed 5-*endo*-dig cyclisation to promote regioselective 6-*endo* cyclisation under mild conditions. Naturally occurring alkaloids containing the 11*H*-indolo[3,2-*c*]quinoline scaffold have diverse biological properties.[12]



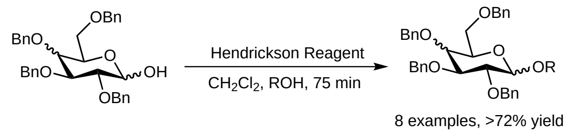
(C) Isoquinoline and β-carboline are important scaffolds in naturally occurring and synthetic bioactive alkaloids. As an alternative to the Pictet–Gams reaction, Wu and Wang have developed a one-pot protocol to access isoquinoline and β-carboline. The Hendrickson reagent is used to trigger cyclization which is then followed by oxidative aromatization.[13]



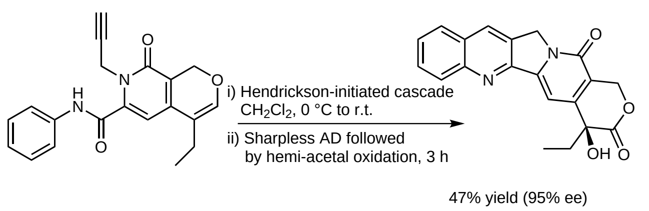
(D) Xu and co-workers have described an efficient synthesis of furoquinolinones using a Hendrickson reagent initiated cascade annulation involving the conversion of stable aniline-amides to the corresponding highly reactive imido-carbonium intermediates.[14]



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



(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 trimethyloxonium fluoroborate was used as the activating agent.[17]



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