J. prakt. Chem. 338 (1996) 684–686

Journal für praktische Chemie
Chemiker-Zeitung

Betmip (1-(Triphenylphosphorylideneaminomethyl)benzotriazole), A Unique CH_2=N–$PPh_3^+X^-$ Equivalent for Organic Synthesis

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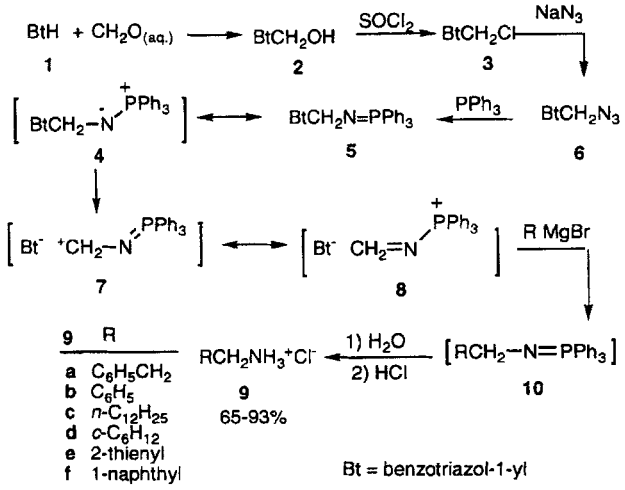
Received May 22nd, 1996

Since the first syntheses of iminophosphoranes from tertiary phosphines and organic azides [1], numerous articles have described the synthetic applications of such N=P compounds [2–4]. We discuss betmip **5**, 1-(triphenylphosphorylideneaminomethyl)benzotriazole, a $^+CH_2N{=}PPh_3$ or $CH_2{=}N{-}P^+Ph_3$ synthon equivalent (an analog of vinyltriphenylphosphonium halide, $CH_2{=}CH^+PPh_3\ X^-$) for the generation of *N*-alkyliminophosphoranes and novel α-functionalized *N*-alkyliminophosphoranes. Betmip **5** is prepared from inexpensive aqueous formaldehyde and benzotriazole in four simple steps (Scheme 1) [5, 6], each affording a stable solid product in quantitative yield. The name betmip **5** consists of „bet", „m", „i", and „p" which represent „benzotriazole", „methylene", „imino", and „phosphine", respectively.

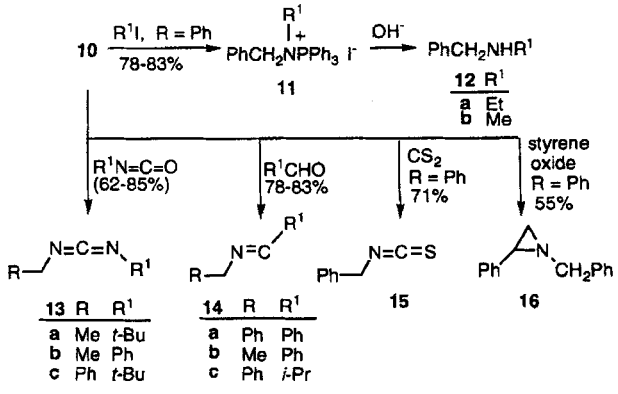
Betmip **5** contains both an electrophilic methylene carbon and a nucleophilic nitrogen atom. Nucleophilic substitution on the methylene carbon displaces benzotriazole with formation of a nucleophile–carbon bond, while reaction of an electrophile at the N=P group forms a nitrogen–electrophile bond. The nucleophilic and electrophilic centers of **5** mutually interact allowing easy formation of the ion pairs **7** and **8** as shown in Scheme 1, a lower reactivity of N=P towards electrophiles than for other iminophosphoranes, and easier displacement of the benzotriazole by nucleophiles as compared to other benzotriazole Mannich derivatives. Thus betmip **5** has good stability, allowing prolonged storage.



Scheme 1

Grignard reagents transform betmip **5** into iminophosphoranes **10** [5] which undergo hydrolysis during work-up to give amines. Thus, betmip **5** provides a convenient $^+CH_2NH_2$ synthon equivalent for conversion of a carbanion to an one-carbon higher homologous primary amine. *N,N*-Bis(trimethylsilyl)methoxymethylamine, the only similar synthon equivalent [7, 8], is prepared from hexamethyldisilane and carcinogenic chloromethyl methyl ether. Product yields are significantly higher by the betmip method than using *N,N*-bis(trimethylsilyl)methoxymethylamine.

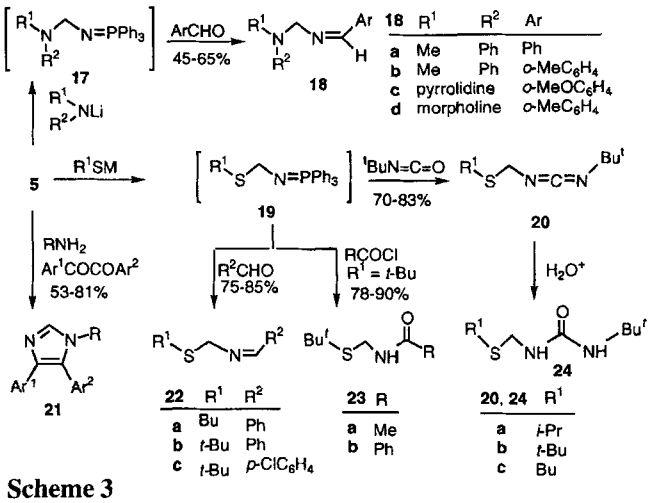
In situ treatment of the same intermediates **10** with allkyl iodides gave **11**, easily hydrolyzed to secondary amines **12**. Similarly, **10** with an isocyanate, an aldehyde, carbon disulfide, or styrene oxide afforded in high yield unsymmetrical carbodiimides **13**, Schiff bases **14**, isothiocyanates **15**, and aziridines **16** (Scheme 2) [6]. These reactions can be carried out in one-pot from **5**, without isolation of iminophosphoranes **10**, with straightforward work-up. The by-prod-



Scheme 2

uct benzotriazolate is easily removed during aqueous work-up and could be recovered for reuse.

N-(α-Heteroatomalkyl)-substituted iminophosphoranes had not been reported prior to the discovery of betmip **5**. Treatment of betmip **5** with lithium amides formed *N*-(α-dialkylaminomethyl)iminophosphoranes **17**, which were converted by arylaldehydes to novel α-(arylideneamino)alkylamines **18** (Scheme 3) [9]. Similarly, *N*-(α-alkylthiomethyl)iminophosphoranes **19**, conveniently prepared by reaction of betmip **5** with thiolates, were transformed without isolation into four novel classes of functionalized formaldehyde-*N*,*S*-acetals [10]; *N*-(alkylthiomethyl)-*N'*-alkylcarbodiimides **20**, *N*-(alkylthiomethyl)benzalimines **22**, *N*-(alkylthiomethyl)amides **23** and *N*-(alkylthiomethyl)-*N'*-alkylureas **24** (Scheme 3).

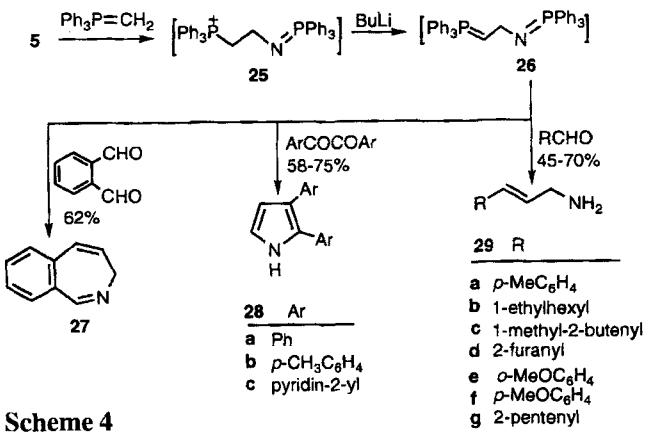


Scheme 3

Primary amines and α-diaryl ketones convert betmip into 1,4,5-trisubstituted imidazoles **21** in good yield [11]: this is the first method to synthesize 1,4,5-trisubstituted imidazoles from α-diketones.

Bis(alkylidenetriphenylphosphoranes) (1,2-, 1,3-, and 1,4-bisylides) and bis(iminophosphoranes) have been known for decades [2, 6, 12]. However, the chemistry of monoazabisphosphorus ylides containing both an iminophosphorane and a phosphorus ylide was unexplored prior to betmip chemistry. Nucleophilic reaction of betmip **5** with methylidenetriphenylphosphorane followed by treatment with butyl- lithium gave 1-aza-1,3-bis(triphenylphosphoranylidene) propane **26**, the first 1,3-monoazabisylide (Scheme 4) [13, 14]. *In situ* treatment of the 1,3-monoazabisylide **26** with phthalic dicarboxaldehyde afforded 3*H*-2-benzazepine **27** in 62% yield. Wittig/aza-Wittig reactions of **26** with α-diketones gave 2,3-disubstituted pyrroles **28** in 58–75% yield. The different reactivity of the two functionalities in **26** with aldehyde allowed the development of an efficient new synthetic method for primary allylamines **29**. Thus, treatment of **26** with one equivalent of aldehydes gave primary allylamines **29** in high steric selectivity in 45–75% yields (Scheme 4).

Similarly, nucleophilic displacement of benzotriazole from **5** with anion **31** (from dimethyl phosphite and butyllithium) gave intermediate **32**, a precursor of 1,2-monoazabisylide equivalent (Scheme 5) [13, 15]. Intermediate **32** was converted

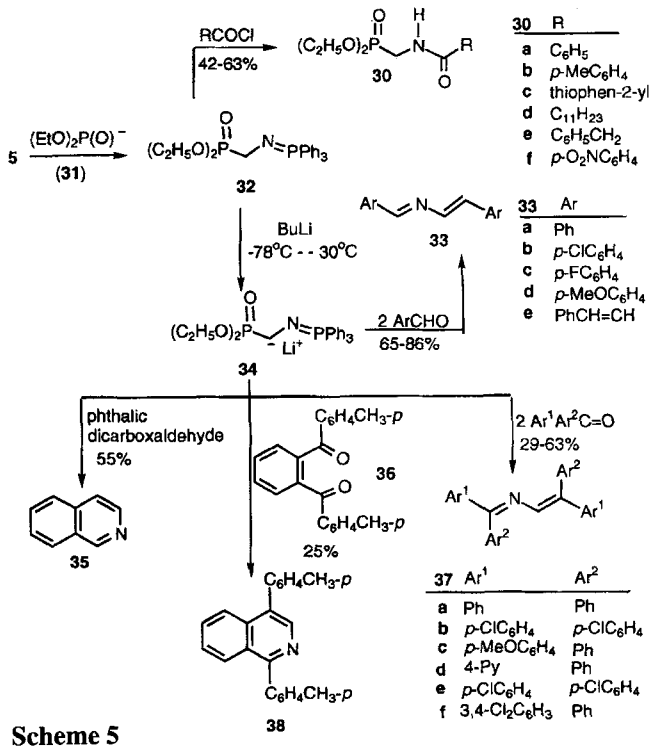


Scheme 4

by acyl chlorides into diethyl [(acylamino)methyl]phosphonates **30**.

The methylene group in **32** can also be deprotonated by butyllithium at –30 °C to generate phosphonate carbanion **34** (a 1,2-monoazabisylide equivalent). Treatment of **34** with two equivalents of an aldehyde gave 2-azabutadienes **33** (Scheme 5). However, intermediate **32** reacts with a single molar equivalent of an aldehyde to give the 1:2 product **33** because one equivalent of **32** is consumed in a Horner-Wittig step. Horner-Wittig/aza-Wittig reaction of **34** with diaryl ketones, phthalic dicarboxaldehyde or diketones afforded 1,1,4,4-tetraarylbutadienes **37** and isoquinolines **35**, **38**, respectively.

In conclusion, betmip as the first CH_2=N-P^+Ph_3 X^- aza-Wittig analog provides a new carbanion route to iminophosphoranes and convenient synthon equivalents of $^+CH_2NH_2$ and $^+CH_2N$=. Betmip also allows for the first preparation of



Scheme 5

new α-heteroatom-alkyl iminophosphoranes and 1,2-monoazabisylide equivalents. The synthetic utility of betmip has been illustrated by the convenient synthesis of a broad spectrum of nitrogen-containing compounds and heterocycles.

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