Extremely Strong, Non-ionic Bases: Syntheses and Applications**

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Dedicated to Professor Albert Eschenmoser on the occasion of his 60th birthday

Abstract: Monomeric and polymeric peralkylated triamino(imino)phosphoranes have been synthesized from inexpensive starting materials. The monomers are inert, distillable liquids that exhibit a basicity of up to 10000 times the basicity of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Applications in organic synthesis are presented, advantages over common bases discussed.

For simplicity of handling and mildness of reaction conditions, non-ionic nitrogen bases are widely used reagents or catalysts. As weak to medium strong bases, a great variety of non-ionic bases of low to very high steric hindrance are available, e.g. pyridine, 2,6-di-*tert*-butylpyridine[1], 1,4-diazabicyclo[2.2.2]octane, 1,2,2,6,6-pentamethylpiperidine, 1,8-bis(dimethylamino)-naphthalene («proton sponge»)[2], 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[3], 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[4], 3,3,6,9,9-pentamethyl-2,10-diazabicyclo-[4.4.0]dec-1-ene[5], 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)[6], 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), and polymer bound TBD. Despite the advantages of non-ionic versus ionic bases, hardly any efforts are reported to synthesize and applicate non-ionic bases stronger than DBU or DBN, with exception of some highly hindered guanidine bases[7].

One essential requirement for a useful non-ionic base – low affinity to any other particle than protons – is probably only met by amine- and imine-bases. As the most promising principle for constructing very strong bases of high chemical stability, deprotonation of highly charge-delocalized systems was pursued. Indeed, the long known iminophosphorane **1a**[8] proved to be ca. 300 times more basic than pentamethylguanidine and, in contrast to earlier literature reports, chemically exceptionally stable; structure variation of this system, e.g. **1b** (Scheme 1), thus seemed to be a promising route to new, versatile non-ionic nitrogen bases.

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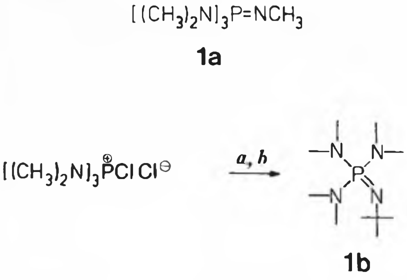
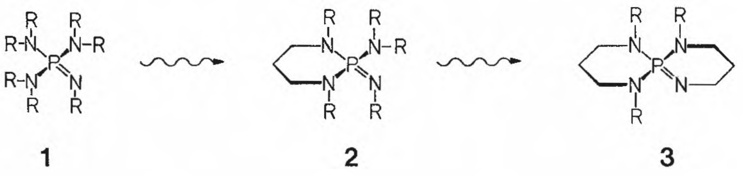


Scheme 1. a: t-BuNH$_2$/CH$_3$CN (130°C); b: NaOH. **1b**: *b.p. 62°C/0.01 Torr,* **1b**·*HPF$_6$*[9]*: m.p. > 310°C (decomp.).*

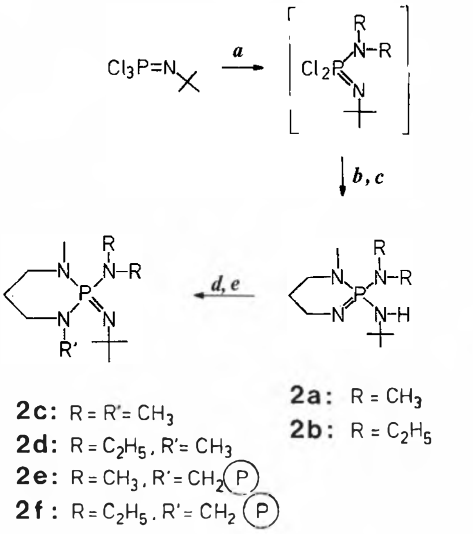
For enthalpic (improved conjugation in the cation) as well as for entropic reasons, cyclized derivatives, especially with sixmembered rings, e.g. **2** and **3**, were expected to show enhanced basicity (Scheme 2).



Scheme 2

Since no cyclic triamino(imino)phosphoranes have been reported to date, efficient methods for their synthesis had to be developed.

Readily available *tert*-butylimino-phosphorus trichloride[10] was converted to **2a** or **2b** in 60% yield in a one-pot reaction (Scheme 3). Regioselective methylation of **2a, b** produced **2c, d** in over 90% yield.



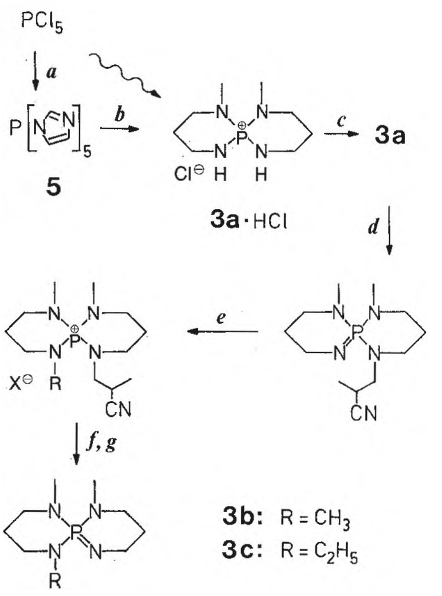
Scheme 3. a: Me$_2$NH / Et$_3$N / CH$_2$Cl$_2$ (−50°C, **2a**) *or Et$_2$NH / Et$_3$N / CH$_2$Cl$_2$ (20°C,* **2b**)*, respectively; b: H$_2$N(CH$_2$)$_3$NHCH$_3$ (*__4__*) (20°C); c: NaOH; d: CH$_3$Cl (0°C,* **2c, d**) *or Ⓟ-CH$_2$-Cl (20°C–reflux,* **2e, f**)*, respectively/CH$_3$CN/THF; e: NaOH (*__2c, d__*) or* **2a–d, 1a** *(*__2e, f__*), respectively.* **2a**: *b.p. 92°C/0.01 Torr,* **2a**·*HPF$_6$: m.p. 208–209°C;* **2b**: *b.p. 83°C/0.025 Torr,* **2b**·*HPF$_6$: m.p. 172–174°C;* **2c**: *b.p. 58°C/0.04 Torr,* **2c**·*HPF$_6$: m.p. > 310°C (decomp.);* **2d**: *b.p. 74°C/0.03 Torr,* **2d**·*HPF$_6$: m.p. ca. 300°C (decomp.)*[9].

1b, **2c**, and **2d** are inert, distillable liquids, partially or completely miscible with all common solvents. **2d** has some advantages compared with **1b**: **1b** must be formed in a pressure reaction, **2d** is easily available in mole scale, can be bound to polystyrene via **2b**, and is a stronger base (see Table 1).

Scheme 4 shows the synthesis of bicyclic system **3**. Whereas direct reaction of the diamine **4** with phosphorus pentachloride mainly produced polymeric material, the newly prepared **5** (structure not proved) cleanly reacted with **4** to afford **3a**·HCl in 70% yield. Direct monoalkylation being unsatisfactory, an alternative route was devised which leads to **3b, c** in more than 90% yield (**3b** solid, **3c** distillable liquid, miscible with all common solvents).

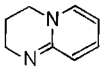
In Table 1 the new triamino(imino)phosphorane bases are compared with other commercially available or known bases with respect to:

- the relative basicity in acetonitrile[11];
- the relative steric hindrance expressed as relation of alkylation to elimination in the reaction with isopropyl bromide;
- the half-life in 1 M water solution;
- the half-life with benzaldehyde in 1:1 molar ratio without solvent (a measure for the reactivity towards carbonyl compounds).

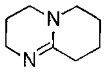


Scheme 4. a: imidazole/Et$_3$N/pyridine/CH$_2$Cl$_2$ (10°C); b: **4**/*pyridine (20–240°C); c: NaOH; d: CH$_2$=C(CH$_3$)CN/THF (20°C); e: CH$_3$Cl (*__3b__*) or C$_2$H$_5$Br (*__3c__*), respectively/CH$_3$CN (0°C); f: NaOCH$_3$/MeOH; g: 160°C/0.1 Torr.* **3a**: *b.p. 105°C/0.02 Torr,* **3a**·*HPF$_6$: m.p. 102–103°C;* **3b**: *b.p. 84°C/0.03 Torr, m.p. 68–71°C,* **3b**·*HPF$_6$: m.p. > 230°C (decomp.);* **3c**: *b.p. 83°C/0.03 Torr,* **3c**·*HPF$_6$: m.p. ca. 270°C (decomp.)*[9].

Clearly **2d** and **3c** are especially interesting for synthetic purposes.



6[12]



7[13]

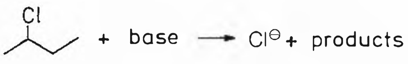
TMG = tetramethylguanidine
PMG = pentamethylguanidine[14]

Table 1.

base	rel. basicity	rel. steric hindrance	$t_{1/2}$(H$_2$O)	$t_{1/2}$(C$_6$H$_5$CHO)
TMG	< 0.06			
DBN	0.063 ± 0.0025	12	< 1 min/22°C	0.45 h/60°C
6	0.098 ± 0.0015	0.64	2.25 h/100°C	≫ 1 h/150°C
DBU	0.214 ± 0.0025	0.27	1.75 h/22°C	1.5 h/100°C
7	0.381 ± 0.0035	0.67		
PMG	1	1.9	4 h/22°C	20 h/160°C
MTBD	2.75 ± 0.035	0.09	4.8 h/22°C	> 15 h/180°C
TBD	9.39 ± 0.15			
1b	80.9 ± 3.5	≪ 0.001	very stable	4.5 h/200°C
1a	ca. 300	0.15	very stable	1.6 h/100°C
2c	322 ± 15	≪ 0.001	very stable	2 h/200°C
2d	433 ± 15	≪ 0.001	very stable	9 h/200°C
3c	2017 ± 70	0.96	> 2 h/160°C	0.8 h/75°C

Applications of **1a**, **2d**, *and* **3c**

With regard to steric hindrance, **3c** (7-ethyl-5,11-dimethyl-1,5,7,11-tetraaza-6-phosphaspiro[5.5]undec-1(6)-ene) lies in between DBN and DBU. The extremely high basicity makes it a very efficient, mild dehydrohalogenation reagent (Scheme 5).

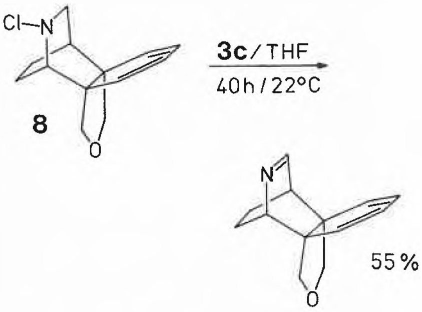


Scheme 5.

base	*k* (rel.)
DBU	1
3c	400
0.56 M *t*-BuOK/DMSO	ca. 33000[15]

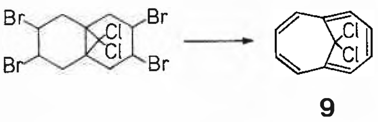
In relation to its basicity, **3c** is quite resistant towards carbonyl compounds (aza-Wittig-reactivity) as compared with DBN and DBU (enamine reactivity). For that reason **3c** is far superior to DBN, DBU, or *t*-BuOK in reactions involving esters, ketones, and aldehydes.

HCl is eliminated from **8** at room temperature[16] (Scheme 6); DBN/DBU are unsuitable due to rapid reaction with «positive halogen».



Scheme 6

For the conversion in Scheme 7, **3c** is too nucleophilic; yield of the thermally instable annulene **9**[17] is best with more hindered **1a**.

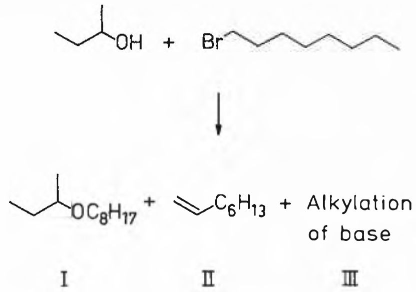


Scheme 7.

base	yield of **9**
DBN	6%[17]
DBU/THF/20°C/4d	40%
1a/THF/20°C/2d	72%

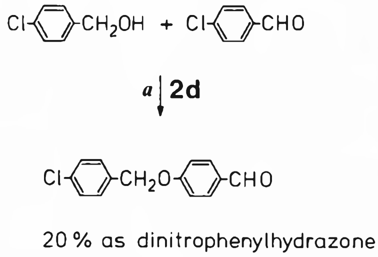
So far even more useful seems the highly hindered and chemically exceptionally stable iminophosphorane **2d** (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine, BEMP), suitable as catalyst in reactions where deprotonation is not rate-determining, especially for alkylations and acylations. At room temperature, **2d** is stable towards aggressive reagents such as CCl_3COCl, $CSCl_2$, $POCl_3$, $SOCl_2$, *p*-toluenesulfonylchloride, PCl_5, $TiCl_4$, dry CO_2, I_2, $(CH_3)_3SiCl$, and alkyl halides except methyl halides. It deprotonates substantially e.g. acidic alcohols like polyols, benzylic and propargylic alcohols, nitroalkanes, cyclopentadiene, carboxylic acid amides and thioamides in acetonitrile solution. Its basic power is comparable to the system 5 M aqueous $KOH/Bu_4N^{\oplus}/CH_3CN$ and somewhat higher than that of the system K_2CO_3/18-crown-6/CH_3CN[18], many phase transfer procedures could thus be replaced by reaction with **2d** under strictly anhydrous conditions.

Scope and limitations of **2d** as base are manifested in two «prototype» reactions: the low rate of elimination side reactions (Scheme 8), its high thermal and chemical stability, and the extremely low rate of hydride transfer reactions compared to alkali bases (Scheme 9), the main pathway for basic racemisation of alcohols[19].



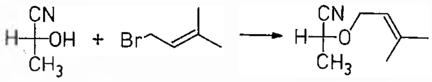
Scheme 8.

base	I	II	III
K/Cryptand [2.2.2][20]	32%	64%	
75% $NaOH/Bu_4N^{\oplus}Br^{\ominus}$	65%	25%	10% (Oct_2O)
2d	62%	2%	36%



Scheme 9. a: 1 milliequivalent ethylenediaminetetraacetic acid (EDTA)/180°C/teflon vessel; $t_{1/2}$*:* $Bu_4N^{\oplus}$ *ca. 15 min,* $Bu_4P^{\oplus}$ *< 1min,* $Ph_4P^{\oplus}$ *< 1 min. – Note: Addition of potassium nonaflate/18-crown-6 in 1:1.2 molar ratio to the reaction mixture causes a rapid Claisen-Tishtshenko-disproportionation of the aldehyde (*$t_{1/2} \approx 20–30$ *s). The sensitivity of the reaction to traces of metal ions is so high, that yield drops to less than 10% when acid-treated glassware is used as reaction vessel. In this medium none of the common organic cations would be stable enough; except perhaps by employing cryptands, there would probably be no other possibility to catalyze such a reaction.*

In reactions involving unstable anions, as in Scheme 10, a homogeneous medium is far more convenient than a two phase system.



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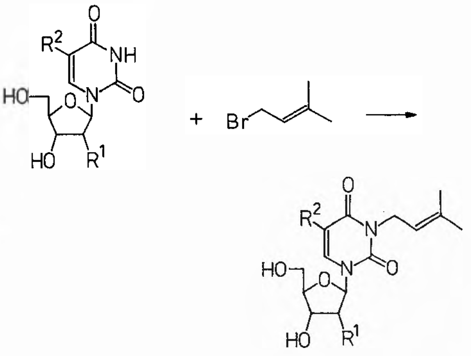
Scheme 10.

base/solvent	yield of **10**
30% $NaOH/CH_3Oct_3N^{\oplus}Cl^{\ominus}/CH_2Cl_2$	32%[21]
2b/CH_3CN	73%

With **2d** as base, thymidine and uridine can be alkylated in homogeneous solution (Scheme 11). Due to the higher regioselectivity of the alkylation, yields are better than those obtained by a solid-liquid phase transfer reaction:



11a: $R^1 = H$, $R^2 = CH_3$
11b: $R^1 = OH$, $R^2 = H$

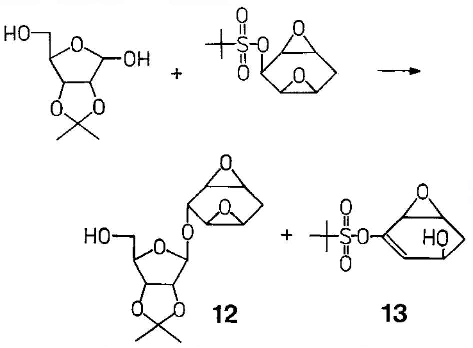
Scheme 11.

base/solvent	yield of **11**
K_2CO_3/18-crown-6/CH_3CN	55% **11a**
2d/CH_3CN	81% **11a**
2d/DMF	55% **11b**

The relatively rate of elimination in reactions involving **2d** as compared to solid-liquid phase transfer reactions is demonstrated by the glycosidation shown in Scheme 12[22].

With alkali bases the proportion of the elimination product **13** is much higher than with **2d**.

Ethylmalonic dimethylester is alkylated with ethyl iodide in presence of **2d** without solvent in homogeneous solution at room temperature (Scheme 13).



Scheme 12.

base/conditions	yield of **12**
t-BuOK/t-BuOH/CH_3CN/50° C	23%
K_2CO_3/18-crown-6/CH_3CN/75° C	34%
2d/75° C	60%

Scheme 13

10% excess of alkyl halide and base is sufficient to produce a product of 99% purity (GC).

The polymer bases **2e** and **2f** prove to be extremely stable, versatile heterogenic catalysts or reagents. The protonated polymers can easily be converted to the free bases by treatment with a suitable iminophosphorane base.

The extremely high stability of the triamino(imino)phosphorane bases towards hydrolysis make them interesting catalysts for aldol condensations and reactions where hydroxide ions are required in organic medium at elevated temperatures.

Typical procedure for an alkylation with **2d** *as base:* 1 mmol thymidine and 1.1 mmol **2d** are dissolved in 5 mL CH_3CN, 1 mmol isopentenyl bromide is added and the mixture kept at room temperature for 96 h. The reaction mixture is poured into 50 mL 1 M phosphate buffer and the product extracted with three 20 mL portions of ethyl acetate. Evaporation of the solvent, preparative thick layer chromatography (ether/MeOH 6:1), and crystallization from ether gives **11a**, *m.p.* 92–94°C, total yield 81%.

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