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Novel Gabriel Reagents†

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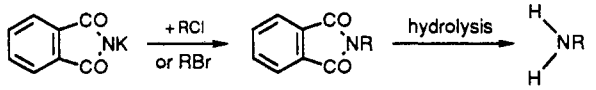
The classical method for synthesis of primary amines, which involves alkylation of potassium phthalimide followed by cleavage of the phthaloyl protecting group, was developed by Siegmund Gabriel (1851–1924; German chemist; born in Berlin; Ph.D. in Heidelberg (Bunsen); University of Berlin)[1,2] more than a century ago and is mentioned in most textbooks dealing with organic chemistry. Since then the experimental pro-



cedure has undergone several improvements with respect to both the alkylation and cleavage steps.[3] Thus various solvents have been introduced, allowing the reaction to take place at a lower temperature than that originally used, and novel alkylating agents have also been applied. In addition, alternative conditions for hydrolysis and cleavage such as hydrazinolysis were developed, but there is no doubt that the regeneration of the amine formed often presents considerable practical problems,[4-7] and in cases when neither strong acid or base nor hydrazine can be applied, this reaction cannot be used. Until recently, much less work was devoted to the search for substitutes for phthalimide itself, but now a number of such reagents are available, allowing cleavage afterward under a variety of mild alternative conditions.

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Phthalimide efficiently excludes dialkylation. Hendrickson and co-workers generalized the Gabriel synthesis to include reagents allowing also dialkylation but not polyalkylation to take place.[8] Their concept involves the use of two monovalent protecting groups[9] (P^1 and P^2) instead of a divalent one, and its full implementation leads to secondary amines, whereas primary ones can still be obtained. It requires protected compounds, **1**, here called Gabriel reagents to indicate that they have been developed or applied to replace phthalimide or its potassium salt in the Mitsunobu[10] or Gabriel reactions. In this context they will be

$$\underset{\mathbf{1}}{HNP^1P^2} \xrightarrow{+R^1X} R^1NP^1P^2 \xrightarrow[+R^2X]{-P^2} R^1R^2NP^1 \xrightarrow{-P^1} R^1R^2NH$$

classified according to the nature of the P^1 and P^2 groups, forming integral parts of the reagents. The synthesis, properties, and use of these imides will be the major topic of this Account, mainly stressing the development that has taken place after Gibson and Bradshaw wrote their review.[3] In addition, recent

† Abbreviations: The symbols of protecting groups are in accordance with the 1983 Recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.* **1984**, *138*, 9).

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(2) Colman, J.; Albert, A. *Ber. Dtsch. Chem. Ges.* **1926**, *59A*, 7.
(3) Gibson, M. S.; Bradshaw, R. W. *Angew. Chem.* **1968**, *80*, 986; *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919 (review).
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(10) Mitsunobu, O. *Synthesis* **1981**, 1 (review).

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progress in the alkylation of various types of amides (P^2 = H or alkyl) will be briefly discussed from a preparative point of view. This field was carefully reviewed previously by Challis and Challis.[11] From the alkylated amides the corresponding amines can be more or less easily regenerated.

Imide Types of Reagents Investigated

Imidodicarbonates. (P^1 and P^2 are both alkoxycarbonyl residues.)

Symmetrical Imidodicarbonates. The first useful derivative of this type, di-*tert*-butyl imidodicarbonate ($P^1 = P^2$ = Boc) (**2**), was prepared by Carpino[12] from (*tert*-butoxyoxalyl)hydrazine via a Curtius rearrangement of the corresponding azide. The yield in this step

$$\underset{\mathbf{2}}{HN(Boc)_2} \quad \underset{\mathbf{3}}{HNZ_2} \quad \underset{\mathbf{4}}{HN(Boc)C(O)OMe} \quad \underset{\mathbf{5}}{HNZ(Boc)}$$

(Boc = C(O)O-*t*-Bu, Z = C(O)OBzl)

was 24%. The product was applied for direct conversion of a benzylic bromide as well as of a bromoacetate ester, with the aid of sodium hydride, to benzylic amine and glycine ester, respectively, by acidic cleavage of the two Boc groups.

An improved approach to compound **2** was obviously required,[13] and there are a few interesting attempts in this direction in the literature.[14-16] Among these, Jones et al.[15] showed that *tert*-butyl oxamate, easily available on a large scale, can be oxidized with $Pb(OAc)_4$ in *t*-BuOH, no doubt with the formation of *t*-butoxycarbonyl isocyanate in situ,[17,18] to give the product in 70% yield.

In our laboratory, starting from formamide we have exploited exhaustive *tert*-butoxycarbonylation,[19-22] with 2 equiv of commercially available di-*tert*-butyl dicarbonate (Boc_2O) and catalytic amounts of 4-(dimethylamino)pyridine (DMAP), for a large-scale, one-pot synthesis of **2** with simultaneous removal of the formyl group of the starting material.[23] This method is now also used commercially.[24] More recently, the same procedure has been used to make the ^{15}N-labeled derivative.[25]

The potassium salt of **2** has been isolated[26] and used for Gabriel type alkylations with the isolation of the protected primary products.[23,26-28] The same applies to the sodium salt.[29] In addition to these salts, the lithium salt, generated in situ with *n*-butyllithium, was first applied by Åkermark et al.[30] to palladium-catalyzed allylic amination. These authors also showed that one Boc group can be removed selectively from the products in the presence of minute amounts of trifluoroacetic acid. More recently, however, they used the sodium salt of **2** in a new methodology for the synthesis of protected, primary pentadienylamines.[31] Compound **2** has also been explored in the context of asymmetrical allylic amination.[32]

Another symmetrical compound of this type, dibenzyl imidodicarbonate (**3**), was made by the addition of benzyl alcohol to benzyloxycarbonyl isocyanate, together with a whole series of unsymmetrical derivatives which will be discussed in the next section.[33] This compound was also prepared recently directly from benzyl carbamate and benzyloxycarbonyl chloride in the presence of potassium hydride.[28] The potassium salt was used for alkylation purposes.

Unsymmetrical Imidodicarbonates. *tert*-Butyl methyl imidodicarbonate (**4**) was made as described above for **2** by $Pb(OAc)_4$ oxidation of *tert*-butyl oxamate in methanol.[15,17] Its potassium salt was isolated and used in Gabriel type alkylations to give the corresponding substituted *tert*-butyl methyl imidodicarbonates, which could be selectively cleaved with NaOH at 20 °C to give pure substituted *tert*-butyl carbamates in 71–73% yields. Compound **4** is no doubt worth further consideration in cases in which treatment with NaOH is acceptable.

Benzyl *tert*-butyl imidodicarbonate[34] (**5**) was first prepared by starting from benzoyl isocyanate and benzyl alcohol. The product was exhaustively *tert*-butoxycarbonylated[19-22] to give in situ benzyl *tert*-butyl *N*-benzoylimidodicarbonate, which was aminolyzed directly to **5**. The sodium salt was prepared in quantitative yield, characterized, and subsequently used in a few simple Gabriel alkylations, giving products in 86–93% yields. Free **5** was used in two Mitsunobu reactions with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD), giving products in only slightly lower yields.

N-Alkylated benzyl *tert*-butyl imidodicarbonates are known to cleave selectively by catalytic hydrogenolysis just like ordinary compounds containing simultaneously benzyl and *tert*-butyl carbamate groups.[35] *tert*-Butyl carbamates are also known to undergo N-alkylation,[36] and in principle the same should hold for other alkyl carbamates. Consequently selectively cleavable imi-

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(24) Compound **2** is available from Fluka, item No. 34716.
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dodicarbonates such as **5** open up new possibilities compared with phthalimide for the synthesis of secondary amines by two-step alkylations. As earlier mentioned, one Boc group can also be selectively removed from compounds derived from **2**, and therefore the imidodicarbonate **2** is equally useful.

A whole series of nine alkyl benzyl imidodicarbonates (**6**), including **3** and **5**, was prepared from benzyloxycarbonyl isocyanate and alcohols in yields exceeding 90%.[33] The isocyanate is made from benzyl carbamate

$$\underset{\mathbf{6}}{\mathrm{HNZC(O)OR}} \quad \underset{\mathbf{7}}{\mathrm{H^{15}NZ(Troc)}} \quad \underset{\mathbf{8}}{\mathrm{BzNHZ}}$$

(Troc = $C(O)OCH_2CCl_3$)

and oxalyl chloride in moderate yield. The alcohols were selected in order to enable subsequent cleavage of the alkoxycarbonyl groups in optional order. Most of these mixed imidodicarbonates and a number of additional ones have been applied together with TPP, DEAD, and chiral lactate esters to Mitsunobu reactions.[37] Also a ^{15}N-labeled isocyanate and a ^{15}N-labeled imidodicarbonate of this type, benzyl 2,2,2-trichloroethyl imidodicarbonate (**7**), have been synthesized.[37]

The pK_a values in DMSO of 13 imidodicarbonates have been determined.[38] The values varied between 16.9 for compound **2** and 12.7 for unlabeled **7** with an intermediary one, 14.4, for compound **5**. The yields in Mitsunobu experiments with these reagents could be correlated with their pK_a values, although the syntheses were performed in a different solvent, THF.[38]

With facilitated access by DMAP-catalyzed procedures[19-22,39] as well as by Gabriel and Mitsunobu alkylation of reagents such as **2–5**, the use of imidodicarbonates can be envisaged as becoming practical in the near future. In our own laboratory they have so far been applied preferentially to synthetic work dealing with polyamines[40,41] and amino acids.[42,43]

***N*-Acyl Carbamates.** (P^1 is an acyl and P^2 generally an alkoxycarbonyl residue.)

***N*-Carboxylated Carbamates.** Benzyl *N*-benzoylcarbamate (**8**) was prepared from benzoyl isocyanate and benzyl alcohol and used by Wada and Mitsunobu[44] in combination with TPP and DEAD. It underwent clean N-alkylation with EtOH, *n*-PrOH, and *n*-BuOH in 66–68% yields. With ethyl lactate, a mixture of N- and O-alkylated products was obtained from which, however, pure N-substituted product of inverted configuration could be isolated.[45] In another case, with a protected uridine derivative,[46] a competing O-alkylation took place, too.

Also from compounds of this type, sodium salts can be generated[46] and, consequently, halides can be used for alkylation as in the ordinary Gabriel reaction. In the case of the uridine derivative referred to in the preceding paragraph, this type of alkylation gave exclusive N-alkylation.

The complete 3D structure of a compound related to **8** and that of the corresponding acetyl derivative have been determined.[47] The increased sensitivity of these compounds to cleavage by nucleophiles is reflected in increased acyl CO–N distances by 0.06–0.08 Å. Also the carbamate CO–N bonds appear to be lengthened to nearly the same extent.

***N*-Phosphorylated Carbamates (Phosphoramidates).** Diethyl *N*-(*tert*-butoxycarbonyl)-phosphoramidate (**9**) can be prepared from diethyl phosphoramidate via the corresponding isocyanate, easily obtained with oxalyl chloride.[48] Its sodium salt

$$\underset{\mathbf{9}}{(EtO)_2P(O)NH(Boc)} \quad \underset{\mathbf{10}}{HN(Boc)Tos}$$

is generated with sodium methoxide in quantitative yield and is a nonhygroscopic solid, stable at room temperature. Alkylations with primary alkyl bromides have been performed in boiling benzene in the presence of a phase-transfer reagent. With secondary bromides the reaction is generally incomplete, presumably due to elimination.

Using TPP and DEAD according to Mitsunobu,[49] free **9** has also been used for alkylation of a set of primary and secondary alcohols including a few chiral ones. In the latter case, the reactions took place with essentially complete inversion.

Both protecting groups in **9** are in principle labile to acid. With alkylated derivatives, the corresponding amine hydrochlorides are obtained after saturating benzene solutions with dry HCl and keeping overnight, whereas the Boc group can be removed selectively with trifluoroacetic acid at 0 °C to give the phosphoramidates.[48]

***N*-Sulfonylated Carbamates.** *tert*-Butyl *N*-tosylcarbamate (**10**) was prepared by Weinreb et al.[50] via commercial tosyl isocyanate in 94% yield and used in Mitsunobu alkylation experiments with a number of difunctional substrates in yields normally exceeding 85%. Similar *N*-tosylcarbamates were prepared in our laboratory and applied to Mitsunobu alkylation of lactic acid esters, giving products in higher yields than those obtained with mixed imidodicarbonates.[37]

The pK_a values of compound **10** and two related analogues in DMSO have also been determined.[38] The corresponding values fall in the range 8.5–7.0. Thus, the pK_a values of these compounds together with those of the imidodicarbonates mentioned above span an interval of 10 powers of 10.

N-Alkylated derivatives of **10** can be selectively deprotected,[50] although in some cases the Tos group requires rather drastic conditions.[9] In this context it should also be pointed out that an *N*-Boc group, when present on the same nitrogen atom, exhibits a labilizing effect on Tos on cathodic reduction which can be ex-

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ploited for preparative purposes.[51,52]

***N*-Sulfenylated Carbamates.** In continuation of their previous work dealing with alkylation of bisarylsulfenimides discussed below, Taguchi and Mukaiyama[53] applied the potassium salt of benzyl *N*-((4-chlorophenyl)thio)carbamate for this purpose. With a number of alkyl bromides, benzyl *N*-alkylcarbamates could generally be obtained in yields of 80% or higher over two steps. The sulfur–nitrogen bond of the intermediates is labile to thiols, and the sulfenyl group could therefore be cleaved off with 4-chlorobenzenethiol.

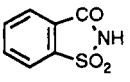
Diacyl Derivatives. *Dicarboximides*. (P^1 and P^2 are both carboxylic acid residues.) Yinglin and Hongwen[54] recently developed a large-scale synthesis of the sodium salt of *N*-formylformamide from formamide and sodium methoxide and alkylated it with various halides and tosylates in CH_3CN or DMF to give the corresponding *N*,*N*-diformylalkylamines in yields above 90%. In one case, with a secondary tosylate, an *N*-monoformyl derivative was isolated instead. The formyl groups could be cleaved off by heating with HCl. One formyl group could be selectively removed by catalytic amounts of KOH in EtOH. Free *N*-formylformamide was first prepared by Allenstein and Beyl,[55] who also performed cleavage experiments with simple alkylated derivatives.

Two simple diacyl imides, i.e., acetyl benzoyl and dibenzoyl imides, have been demonstrated to undergo alkylation with benzyl alcohol under Mitsunobu conditions.[45]

***Sulfenimides*.** Mukaiyama and Taguchi[53,56] alkylated bis-benzenesulfenimide,[57] the synthesis of which obviously requires improvement, via its lithium salt in solvents like tetrahydrofuran with a few primary bromides and 4-toluenesulfonates in 60–86% yields. Two secondary sulfonates also reacted satisfactorily with the imide salt, whereas two alkyl bromides did not. The N-substituted primary products were normally too unstable to be isolated. Their cleavage could in principle be accomplished either with 3 N HCl or benzenethiol. The free imide also added to acrylonitrile and ethyl acrylate to give, after treatment with ethanethiol, the corresponding amino derivatives in respectable yields.

Bis-4-chlorophenylsulfenimide was used similarly.[58] Its lithium salt underwent normal alkylation with 2-(ethoxycarbonyl)ethyl 4′-toluenesulfonate, a reaction that had failed in the case of the unsubstituted sulfenimide, in which case only β-elimination took place due to its high basicity. Some N-alkylated derivatives could also be isolated from this chloro-substituted sulfenimide.

***Saccharin*.** Sugasawa and Abe have introduced saccharin (11) as a replacement for phthalimide in the synthesis of amines by "the saccharin method",[59] particularly to obtain secondary amines. The potassium



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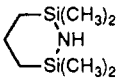

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salt is first monoalkylated, whereupon the imide ring is opened by alkaline hydrolysis to give an N-substituted sulfonamide. After acidification, the product is alkylated a second time. In this step actually 2 equiv of the reagent are consumed, since the carboxylic group in the 2-position also reacts, and this ester is saponified. To isolate the secondary amine, heating with strong acid is required, normally giving products in good yields. The ring opening, second alkylation, and saponification can be performed consecutively without isolation of intermediates. The authors stress that the final hydrolysis takes place much more easily than in ordinary sulfonamides. The saccharin method has later been used by Abe for the synthesis also of diamines,[60] amino alcohols,[60] and less accessible secondary amines.[61,62] The mechanism of the reaction has also been discussed.[63]

The chemistry of 1,2-benzenedisulfonimide has been explored,[64] although in this context rather for retro-Gabriel reactions than as a Gabriel reagent. It is a strong acid. The *N*-benzyl and *N*-phenethyl derivatives are surprisingly inert. The former compound was only partially cleaved with sodium cyanide in DMF at 100 °C or on reflux in 50% ethanol. The latter could be brought to eliminate styrene in low yield.

Miscellaneous Derivatives. The potassium salts of bis(trimethylsilyl)amide, 2,2,5,5-tetramethyl-2,5-disilapyrrolidine, and especially 2,2,6,6-tetramethyl-2,6-disilapiperidine (12) have been proposed as Gabriel reagents for the synthesis of primary amines by Hosomi et al.[65] Compound 12 can be prepared in four steps from allyltrimethylsilane and is then treated with KH in THF and subsequently alkylated. The yields in the last step are in most cases in the range 50–85%. Hydrolysis is accomplished by boiling with 1 M HCl for a few hours.

N-(Benzyloxy)ureas and orthogonally protected *N*-hydroxycarbamates have been proposed to provide *N*-alkyl hydroxyureas and hydroxylamines.[66] *tert*-Butyl *N*-(benzyloxy)carbamate was used in this context.

Alkylation of Amides

This section deals with selected procedures for alkylation of amides which appeared after Challis and Challis wrote their review.[11] Needless to say, from such amides the corresponding amines can be regenerated.

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Thus, phase-transfer-catalyzed N-methylation, *n*-butylation, and benzylation of simple N-substituted formamides have been accomplished by Zwierzak and co-workers.[67] They used a solid–liquid two-phase system containing pulverized $NaOH/K_2CO_3$ in the presence of tetra-*n*-butylammonium hydrogen sulfate in benzene. The yields in the alkylation step were generally higher than 85%, but much material was lost in the subsequent hydrolysis with 10% H_2SO_4. A few N-substituted aliphatic and aromatic carboxamides were alkylated similarly in nearly quantitative yields.[68] Conditions were also described for clean, quantitative mono- and dialkylation of benzamide.[69]

After treatment with potassium hydride, trifluoroacetamides, made from primary amines, have been alkylated with various bromides in THF in the presence of 18-crown-6 as a catalyst to give ultimately secondary amines in high yields.[70]

Zwierzak and Brylikowska-Piotrowicz have shown that N-diethylphosphorylated derivatives of primary amines can be alkylated with excess primary alkyl bromide under phase-transfer conditions and the products subsequently cleaved with HCl in THF at room temperature to give secondary amines.[71] Shortly afterward it was demonstrated that diphenylphosphinic amide could be mono- or dialkylated under similar conditions.[72] For conversion of primary to secondary amines, the authors claim the diphenylphosphinoyl protecting group to be superior to diethylphosphoryl. Secondary alkyl bromides originally gave rise to elimination products, but this problem could be partly overcome by the addition of potassium carbonate and change to a solid–liquid two-phase system.[73]

While benzamide and 4-nitrobenzamide are not acidic enough to undergo the Mitsunobu reaction,[44] as demonstrated with *N*-methyl-4-toluenesulfonamide,[50] sulfonamides in principle react under such conditions, despite competing N-alkylation by DEAD in this case. Alkene, alkyne, and vinylic bromide functions do not seem to restrict this type of reaction, but the reported yields in these cases are generally lower. 4-Toluenesulfonamide itself, however, was not useful.

Sodium salts of sulfonamides, featured in Hinsberg's test[74,75] and in Hinsberg's synthesis of secondary amines,[76] are well-known species. More recently sulfonamides have also been alkylated under phase-transfer catalysis in solid–liquid two-phase systems.[73]

With the aim of cleaving sulfonamides with Zn/acetic acid, Hendrickson and co-workers[8,77] made a set of *N*-alkylbenzoylmethanesulfonamides from benzoylmethanesulfonyl chloride and primary amines whereupon they reacted them with alkyl halides in acetone in the presence of K_2CO_3. Two equivalents of halide were consumed as the phenacyl methylene also underwent alkylation. The Zn/acetic acid regeneration of secondary amines took place in better than 75% yield.

In continuation of their work with benzoylmethanesulfonamides, Hendrickson and co-workers applied triflamide chemistry[78] to alkylation of amines. Trifluoromethanesulfonylation is normally accomplished with triflic anhydride, but more selective protection is sometimes to be obtained with various amides.[79] Alkylation proceeds in acetone at room temperature in the presence of potassium carbonate.[8,80] Secondary amines are obtained after cleavage of the alkylation products, but a strong base such as NaH in DMF with heating and subsequent hydrolysis or reduction with $LiAlH_4$ in ether is required for the elimination of the protecting group. The parent triflamide, however, could not be cleanly monoalkylated, so in order to obtain primary amines, various N-substituted derivatives were used instead. Thus, it is possible to apply *N*-benzyltriflamide, and the benzyl group can also be hydrolyzed off afterward. Therefore this method seems to be of interest mainly for the synthesis of secondary amines.

Concluding Remarks

As demonstrated in this review, during the last two decades a considerable number of compounds have been investigated as substitutes for phthalimide or its potassium salt in the Mitsunobu and Gabriel reactions. Their major advantages are 2-fold: Much milder and rather specific conditions can be used for the final deprotection than are required for phthaloyl, and alkylation can, if required, be carried out twice, in which case also secondary amines are obtained. Several of the novel reagents are easily made, and they can be alkylated in the same way as phthalimide or its potassium salt, but neither strong acid or base nor hydrazine is needed to cleave off the protecting group(s). Besides, the approaches described above to prepare imidodicarbonates and acylcarbamates are in principle rather flexible and should, if necessary, allow additional, selectively protected compounds to be made in the same way. Thus, the imide concept as such has withstood the ravages of time since its introduction a century ago.

In parallel, much work aimed at the direct alkylation of amides has recently been performed, and in many cases it is now possible to obtain specific, relatively simple amides from which the corresponding amines can be regenerated. Many acyl groups used in this context require, however, cleavage conditions which occasionally cannot be tolerated, and the application of carbamates would probably be a better alternative in such cases.

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