A Mild Synthesis of Nitriles by von Braun Degradation of Amides Using Triphenyl Phosphite–Halogen-Based Reagents

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Abstract: A mild procedure for the synthesis of aromatic and aliphatic nitriles is disclosed. In the presence of bromotriphenoxyphosphonium bromide (TPPBr$_2$), *N*-alkyl and *N*,*N*-dialkyl amides undergo von Braun degradation to nitriles in good to excellent yields under the mildest conditions ever reported. The reaction proceeds via formation of an iminoyl bromide intermediate at –60 °C, which subsequently dealkylate upon refluxing in chloroform or even at room temperature. In the case of *N-tert*-butyl, *N*-α-phenylethyl and *N*-benzhydryl amides, chlorotriphenoxyphosphonium chloride (TPPCl$_2$) generated at –30 °C was also effective.

Key words: amide degradation, halotriphenoxyphosphonium halides, imidoyl halides, nitriles, triphenyl phosphite

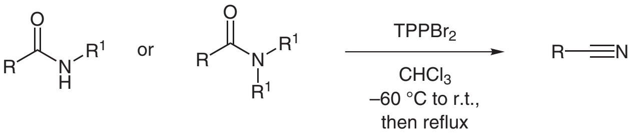
Since the first nitrile synthesis reported by Wöhler and von Liebig as early as 1832,[1] a great deal of research has been devoted to the development of efficient and straightforward processes for the preparation of organic cyanides.[2] Nitriles, in fact, play an important role in organic synthesis as useful substrates for a variety of transformations, and their relevance has increased accordingly along the years.[3] Most recently, nitriles have even featured as partners in alkyne metathesis.[4]

Dealkylation of secondary and tertiary benzamides upon heating in the presence of halogenating reagents is traditionally referred to as the von Braun degradation. Namely, when *N*-alkyl and *N*,*N*-dialkyl amides are treated with inorganic phosphorus halides or thionyl chloride, decomposition into a nitrile and alkyl halide(s) occurs.[5,6] The reaction requires harsh conditions (typically 90–150 °C) and, in addition, the resulting products need to be isolated by distillation from the crude reaction mixture, owing to the formation of otherwise intractable phosphoric tars and byproducts. Because of these drawbacks, the von Braun degradation has found relatively little use for the preparation of nitriles *sensu stricto*, and applications have mainly focused on the alkyl halide product(s) instead, especially for structure elucidation purposes in the alkaloid field.[7] Although slight modifications have been proposed,[8] the reaction conditions still remain quite aggressive, and have limited the usage of this process for synthetic applications. Clearly, if milder reaction conditions were available, the synthetic scope of the von Braun degradation could be extended and the reaction would gain a renewed appeal for the preparation of nitriles.

Recently, we have exploited halotriphenoxyphosphonium halides, viz. $(PhO)_3P^+X\ X^-$ (henceforth TPPX$_2$, where X = Cl or Br), for the activation of a variety of amides into the corresponding iminoyl halides; this has resulted in the development of exceedingly mild protocols for the deacylation of secondary amides,[9a,b] for the synthesis of nitrogen-containing heterocycles such as β-carbolines[9c] and pyrroles,[9d] and also for the dehydration of primary amides into nitriles.[9e]

By close analogy, we envisaged that the remarkable halogenating potential of TPPX$_2$ could be exploited also in the framework of a von Braun degradation which is well known to proceed via an imidoyl halide intermediate.[6b,10] In this paper, therefore, we wish to describe a general method which embodies a von Braun degradation under very mild conditions to convert secondary and tertiary alkyl amides into aromatic and aliphatic nitriles.

To this end, a suitable set of aromatic and aliphatic *N*-alkyl and *N*,*N*-dialkyl amides were synthesized from *p*-toluic acid or 10-undecenoic acid and the appropriate amine following standard literature procedures,[11] and subjected to TPPX$_2$ under typical conditions (Equation 1).[12] In particular, amides **1a**–**x** were treated at –60 °C with a freshly prepared solution of TPPBr$_2$ in chloroform in the presence of triethylamine; in the case of tertiary amides, triethylamine was not included. After warming to room temperature, the reaction mixture was gently refluxed overnight to achieve complete conversion, when necessary, and the crude residue was purified by column chromatography.[13] When TPPCl$_2$ was used, the starting temperature could be raised to –30 °C.[14] The results are summarized in Table 1.



Equation 1 Synthesis of aromatic and aliphatic nitriles by von Braun degradation of secondary and tertiary amides using TPPBr$_2$

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Table 1 TPPX$_2$-Promoted von Braun Degradation of Secondary and Tertiary Amides[a]

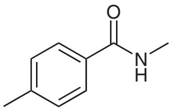
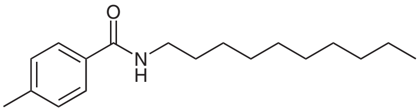
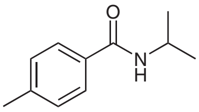
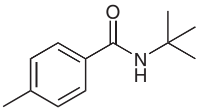
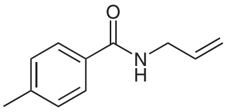
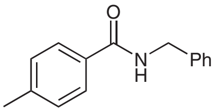
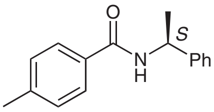
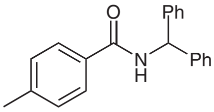
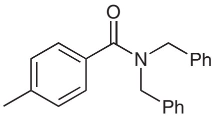
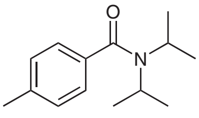
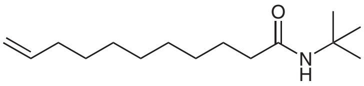
Entry	Substrate	Yield (%)
1	 **1a**	53
2	 **1b**	40
3	 **1c**	80
4	 **1d**	96^{b} (87)^{b}
5	 **1e**	68
6	 **1f**	97 (0)
7	 **1g**	$96^{b,c}$ (90)
8	 **1h**	94^{b} (99)^{b}
9	 **1i**	70^{d} (0)
10	 **1j**	48^{d}
11	 **1k**	61

Table 1 TPPX$_2$-Promoted von Braun Degradation of Secondary and Tertiary Amides[a] (continued)

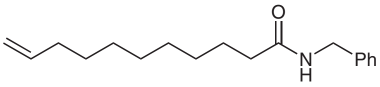
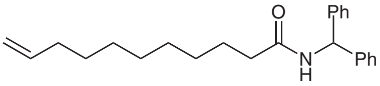
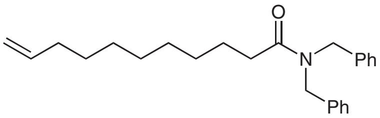
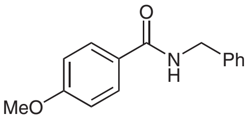
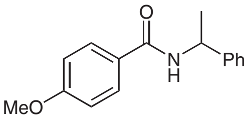
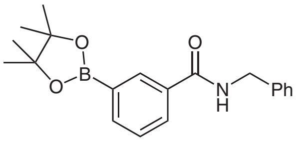
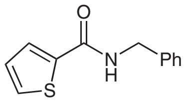
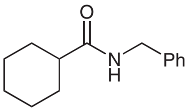
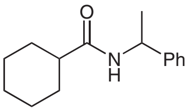
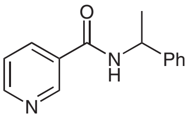
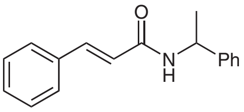
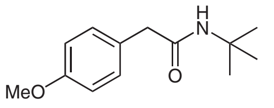
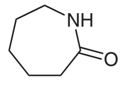
Entry	Substrate	Yield (%)
12	 **1l**	52
13	 **1m**	91
14	 **1n**	55^{d}
15	 **1o**	92
16	 **1p**	96^{b}
17	 **1q**	60
18	 **1r**	62
19	 **1s**	67
20	 **1t**	70^{b}
21	 **1u**	70^{b}
22	 **1v**	88^{b}

Table 1 TPPX$_2$-Promoted von Braun Degradation of Secondary and Tertiary Amides[a] (continued)

Entry	Substrate	Yield (%)
23	 **1w**	49[b]
24	 **1x**	0[e]

[a] Reaction conditions: amide (1.0 mmol), (PhO)$_3$P (1.2 mmol), Br$_2$ (1.2 mmol), Et$_3$N (1.3 mmol), CHCl$_3$ (20 mL), –60 °C to r.t., then reflux for 16 h (unless otherwise noted). Yields in brackets refer to TPPCl$_2$-mediated reactions: –30 °C to r.t., then reflux for 16 h (unless otherwise noted).

[b] Without reflux.

[c] Optically pure amide **1g** was used; in addition to tolunitrile, (*R*)-1-phenylethyl bromide with 25% optical purity was also isolated.[15]

[d] Without addition of Et$_3$N.

[e] Unreacted ε-caprolactam was recovered.

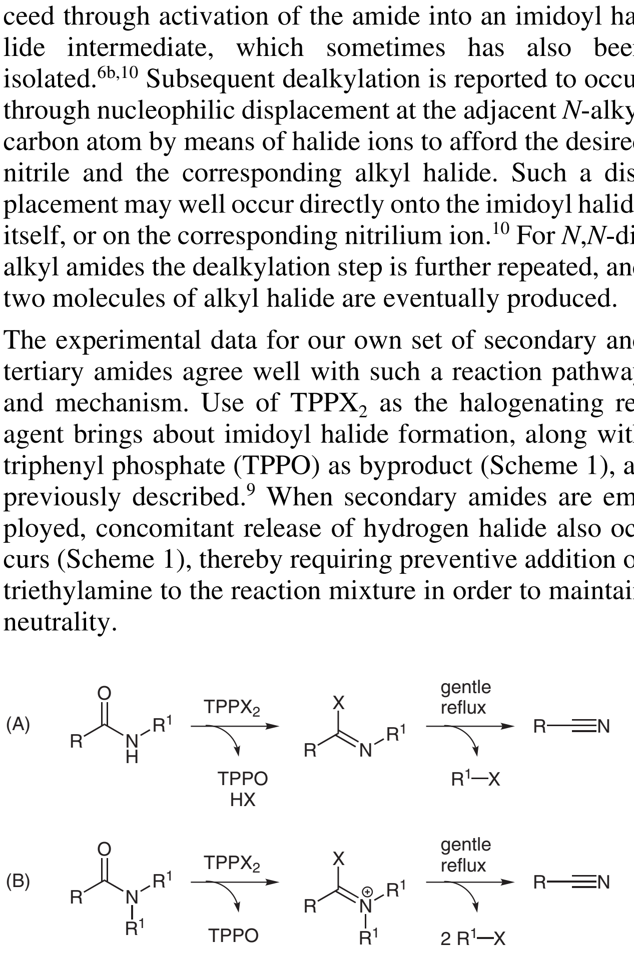
p-Toluamides **1a**–**j** were all converted by TPPBr$_2$ into tolunitrile in moderate to quantitative yields (Table 1, entries 1–10). In the case of secondary amides **1a**–**h** (entries 1–8), excellent yields were obtained for α-substituted *N*-alkyl groups such as isopropyl (**1c**), *tert*-butyl (**1d**), benzyl (**1f**), α-phenylethyl (**1g**), and benzhydryl (**1h**). Most remarkably, dealkylation of secondary amides **1d**,**g**,**h** (entries 4, 7, and 8) proceeded smoothly at room temperature without any reflux. Reaction of *N*-methyl, *N*-decyl and *N*-allyl amides **1a**,**b**,**e** afforded tolunitrile in only moderate yields (entries 1,2, and 5). On the other hand, tertiary amides **1i**,**j** (entries 9 and 10) gave lower yields than the corresponding secondary amides, despite the choice of alkyl substituents that had well performed for the latter such as the isopropyl and the benzyl group. When TPPCl$_2$ was employed, comparable results were obtained for amides **1d**,**g**,**h**, even though yields were generally slightly higher with TPPBr$_2$. However, for benzyl amides **1f** and **1i** the reaction with TPPCl$_2$ failed.

In the case of 10-undecenoyl amides (Table 1, entries 11–14), benzhydryl amide **1m** was converted into 10-undecenenitrile in excellent yield (entry 13), whereas *N*-*tert*-butyl, *N*-benzhydryl, and *N*,*N*-dibenzyl amides (**1k**,**l**,**n**) gave only moderate yields (entries 11, 12, and 14).

On the basis of these results, a further set of *N*-benzyl and *N*-α-phenylethyl secondary amides was prepared to test substrate and functional group compatibility of the TPPBr$_2$-promoted von Braun degradation. Aromatic and aliphatic *N*-benzyl, *N*-α-phenylethyl or *N*-*tert*-butyl amides **1o**–**w** were synthesized from the parent carboxylic acid by reaction of the corresponding acyl chloride with benzylamine, α-phenylethylamine or *tert*-butylamine, and subjected to the action of TPPBr$_2$ under standard conditions.[13] Nitriles were obtained in moderate to excellent yields (Table 1, entries 15–23), especially for aromatic amides. Yet again, use of the α-phenylethyl group as the alkyl substituent at nitrogen allowed to omit the refluxing step and resulted in comparable yields to those of the corresponding *N*-benzyl analogues (compare entry 15 with 16, and 19 with 20). In the case of ε-lactam **1x** (entry 24), treatment with TPPBr$_2$ failed to give the expected ω-bromonitrile, even after prolonged refluxing.

The mechanism of the von Braun degradation has been long since clarified.[6,10] The reaction is well known to proceed through activation of the amide into an imidoyl halide intermediate, which sometimes has also been isolated.[6b,10] Subsequent dealkylation is reported to occur through nucleophilic displacement at the adjacent *N*-alkyl carbon atom by means of halide ions to afford the desired nitrile and the corresponding alkyl halide. Such a displacement may well occur directly onto the imidoyl halide itself, or on the corresponding nitrilium ion.[10] For *N*,*N*-dialkyl amides the dealkylation step is further repeated, and two molecules of alkyl halide are eventually produced.

The experimental data for our own set of secondary and tertiary amides agree well with such a reaction pathway and mechanism. Use of TPPX$_2$ as the halogenating reagent brings about imidoyl halide formation, along with triphenyl phosphate (TPPO) as byproduct (Scheme 1), as previously described.[9] When secondary amides are employed, concomitant release of hydrogen halide also occurs (Scheme 1), thereby requiring preventive addition of triethylamine to the reaction mixture in order to maintain neutrality.



Scheme 1 TPPX$_2$-mediated von Braun degradation of secondary (A) and tertiary amides (B)

As far as the dealkylation of the iminoyl halide is concerned, the greater the ease with which the adjacent *N*-alkyl carbon atom can host a positive charge, the more likely the dealkylation is to proceed via S$_N$1-type mechanism, and the milder the reaction conditions. This is indeed the case for *tert*-butyl, α-phenylethyl and benzhydryl amides such as, for instance, **1d**,**g**,**h**. In fact, complete conversion into the corresponding nitrile was achieved at room temperature without the need to reflux. The monomolecular mechanism is further corroborated by the partial racemization which has been observed for the degradation of optically pure *N*-α-phenylethyl amide **1g** into tolunitrile, resulting also in the isolation of (*R*)-phenylethyl bromide with only 25% optical purity.[15] For *N*-alkyl carbon atoms of secondary, allylic or benzylic nature, as in the case of **1c**,**e**,**f**, competition between S$_N$1- and

S_N2-like mechanism may occur; although yields range to moderate to excellent, complete conversion is accomplished only after heating to reflux. In contrast, yields are lower when the reaction is bound to proceed through bimolecular mechanism, viz. for amides **1a**,**b**.

For amides where the S_N1 mechanism is operative, $TPPBr_2$ can be replaced by $TPPCl_2$ as the halogenating reagent with similar results (see Table 1, entries 4, 7, and 8). When compared to $TPPBr_2$, however, the efficiency of $TPPCl_2$ decreases as long as the bimolecular mechanism tends to prevail, i.e., benzhydryl > α-phenylethyl > benzyl. In fact, whilst degradation of benzhydryl amide **1h** occurred quantitatively at room temperature, α-phenylethyl amide **1g** required heating to reflux, whereas benzyl amides **1f**,**i** failed to give any tolunitrile when treated with $TPPCl_2$, even after prolonged heating at reflux.

The failure of ε-caprolactam (**1x**) to undergo $TPPBr_2$-mediated von Braun degradation is worthy of note, and suggests that this protocol is restricted to acyclic amides. Further, it corroborates the involvement of a nitrilium ion intermediate, whose formation is not permitted in cyclic amides for geometric constraints.

In summary, a variety of aromatic and aliphatic nitriles were prepared from alkyl-substituted secondary and tertiary acyclic amides by von Braun degradation using $TPPBr_2$ as the halogenating species. The dealkylation was carried out under the mildest conditions ever reported in the literature and afforded nitriles in good to excellent yields. This application further demonstrates the synthetic versatility of triphenyl phosphite–halogen-based reagents in functional-group transformations and should be of value as a mild and expeditious access to nitriles from acyclic alkyl amides.

Acknowledgment

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(11) All compounds were characterized by ^1H NMR and EI-MS analysis. For new compounds, ^{13}C NMR and elemental analysis were also performed.

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(13) **$TPPBr_2$-Promoted von Braun Degradation; General Procedure**
Bromine (0.31 mL, 6.0 mmol) was added to a solution of triphenyl phosphite (1.57 mL, 6.0 mmol) in anhyd $CHCl_3$ (20 mL) maintained at –60 °C under argon flow. After addition of dry Et_3N (0.9 mL, 6.5 mmol), the amide (5.0 mmol) was added to the pale orange clear solution (for tertiary amides, however, Et_3N was not used). After leaving to warm to r.t. over a period of 3–4 h, the reaction mixture was gently heated to reflux for 16 h, except when TLC analysis already showed complete disappearance of the starting amide (see Table 1). The solvent was then evaporated under reduced pressure and the resulting nitrile was purified by column chromatography on silica gel.

(14) $TPPX_2$ is generated by reacting triphenyl phosphite with an equimolecular amount of Cl_2 or Br_2 at low temperature, viz. from –30 °C to –20 °C for chlorine or from –60 °C to –50 °C for bromine. Under such conditions, the predominant species is the halotriphenoxyphosphonium halide $(PhO)_3P^+X\,X^-$, which is active for our synthetic scope. When generated at higher temperatures, increasing amounts of the synthetically inactive covalent species dihalo triphenoxyphosphorane $(PhO)_3PX_2$ are also formed.[9a,12]

(15) (a) Reaction of optically pure (*S*)-α-phenylethyl amide **1g**, $[\alpha]_D$ +54.1 (*c* 1.3, acetone); lit.[15b] $[\alpha]_D$ +57.0 afforded tolunitrile along with (*R*)-phenylethyl bromide, $[\alpha]_D$ +28.4 (*c* 2.1, $CHCl_3$); lit.[15c] $[\alpha]_D$ +111.5. (b) Nerdel, F.; Goetz, H.; Wendenburg, J. *Liebigs Ann. Chem.* **1959**, *627*, 106. (c) Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832.