



Pergamon

Tetrahedron Letters 39 (1998) 6387-6390

TETRAHEDRON
LETTERS

Phosphorus in Organic Synthesis. The Tanigawa Reaction Revisited as a Method for Converting Alcohols to Tertiary Amines

Paul Frøyen^a and Jan Skramstad^{b*}

^aDepartment of Biotechnological Sciences, Agricultural University of Norway, P.O. Box 5040, N-1432 Ås, Norway

^bDepartment of Chemistry, University of Oslo, P.O. Box 1033 Blindern, N-0315 Oslo, Norway

Received 9 April 1998; accepted 23 June 1998

Abstract: Contrary to earlier observations, *N*-methyl-*N*-phenylaminotriphenylphosphonium iodide **1** (the Murahashi reagent) does not react with alcohols and primary or secondary amines under mild conditions (80°) to give secondary or tertiary amines. However the reaction can be successfully performed at higher temperatures. A mechanistic scheme implying initial amine exchange between **1** and the added amine leading to the *N,N*-dimethyl analog **5** is suggested. An improved synthesis where the reactive intermediate **5** is formed *in situ* from triphenylphosphine, carbon tetrachloride and HNR³R⁴ is described. © 1998 Elsevier Science Ltd. All rights reserved.

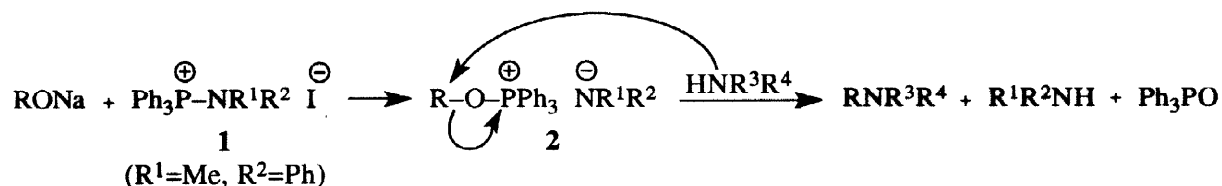
The conversion of an alcohol to the corresponding alkyl or arylamine is an important reaction in synthetic chemistry. Numerous methods[1] have been applied, some direct, others indirect in order to achieve this conversion, but not many combine high yields with convenience. Of the newer methods more frequently cited are the Mitsunobu reaction [2,3], the method of Castro and Selve [4], the procedure of Tanigawa *et al.*[5], of Okada *et al.*[6], and, very lately, the interesting method of Hendrickson *et al.*[7].

In all these reactions the alcohol is activated by a phosphorus compound and the reactions are believed to occur via an alkoxyphosphonium salt. One of us[8] has recently described a convenient one-pot amination of alcohols along a related pathway, where the alcohol is mixed with triphenylphosphine and NBS at low temperature, followed by addition of the amine to be alkylated.

In the present study we revisit the Tanigawa amination [5]. This method has been widely cited in literature for over two decades and is still appreciated by reviewers of amine forming reactions for its combination of convenience with high yields under mild conditions. Originally we intended to investigate the feasibility of using *N*-methyl-*N*-phenylaminotriphenylphosphonium iodide **1** (the Murahashi reagent) for more sophisticated purposes than so far reported, that is as a means of transforming alcohols containing various sensitive functional groups to the corresponding amines, without the destruction of these groups.

In our initial model study, applying triethylamine rather than sodium hydride as a base, we found, however, that treatment of piperonyl alcohol with **1** and diethylamine under Tanigawa conditions (DMF, 80°, 1-2 h) did not yield the expected *N,N*-diethyl-piperonylamine.

Despite this negative result our interest in the Tanigawa reaction was not curtailed, particularly so since the mechanism suggested [5] (*vide infra*), seemed highly improbable and has as its sole justification the fact that it apparently does account for the products.

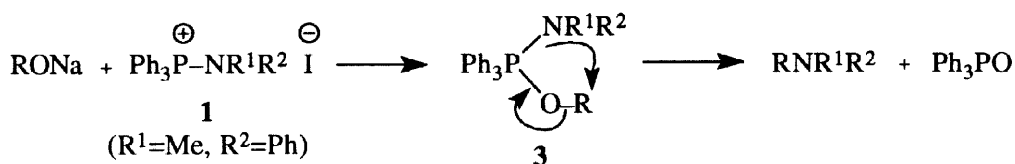


If the proposed intermediate **2** could be realized it would lead exclusively to *N*-methyl-*N*-phenyl substituted amines. This is an obvious consequence of the negatively charged nitrogen of Ph(Me)N which will act as a better nucleophile towards the alkoxyphosphonium entity than the nitrogen of the added R³R⁴NH. Hence no RNR³R⁴ should be formed via **2**. Furthermore, the possibility of a reaction between **1** and DMF/HNR³R⁴ was apparently not considered by the authors [5]. For these reasons a more thorough examination of the Tanigawa reaction seemed called for.

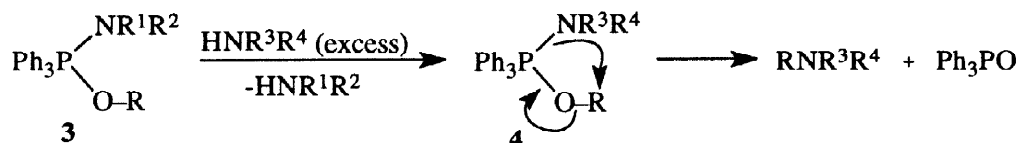
In a series of control experiments we allowed 1-butanol to react with sodium hydride, **1** and diethylamine in DMF under the same conditions as above; thereafter corresponding experiments were performed with benzylamine in place of diethylamine. Both reactions yielded after dilute HCl/NaOH treatments followed by extraction into pentane small amounts of *N*-butyl-*N*-methyl aniline in addition to *N*-methylaniline. Neither *N*-butyl-*N,N*-diethylamine or *N*-benzyl-*N*-butylamine were isolated from or detected in the reaction mixtures.

Finally benzyl alcohol was caused to react with **1** and diethylamine, under Tanigawa conditions as above in DMF as well as in benzene. The reactions afforded in both cases minor yields of two amines only: *N*-methylaniline and *N*-benzyl-*N*-methylaniline. *N*-Benzyl-*N,N*-diethylamine was not detected.

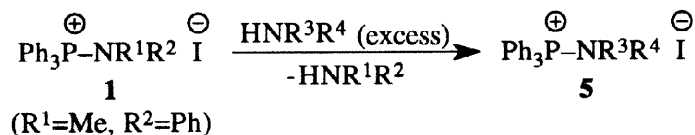
In view of our consistently negative results, the Tanigawa reaction appeared suspect. Contrary to the mechanism suggested by Tanigawa et al. [5], our results indicate a pathway via the pentacoordinated intermediate **3**, implying that the product is independent of the amine applied as nucleophile:



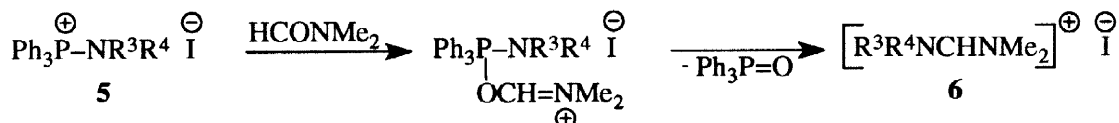
An attractive explanation for the positive results reported [5] is that the aminations were performed at temperatures higher than those stated by the authors. At elevated temperatures **3** could presumably, at least partly, be transformed by HNR³R⁴ into the more reactive intermediate **4**, which under the circumstances decomposes immediately into triphenylphosphine oxide and the expected RNR³R⁴ as shown below.



When the reaction is performed with a weaker base than sodium hydride, e.g., with excess triethylamine present in the reaction mixture, it would appear that the amination might proceed via a mechanism where the added amines HNR³R⁴ react with the Murahashi reagent in an amine exchange reaction forming the required reactant **5** in a first step:



This exchanged Murahashi reagent might subsequently afford the expected amine directly via **4**, or, perhaps more likely in view of the large excess of solvent (DMF), react as shown below via the formamidinium salt **6**, a plausible precursor of RNR^3R^4 .



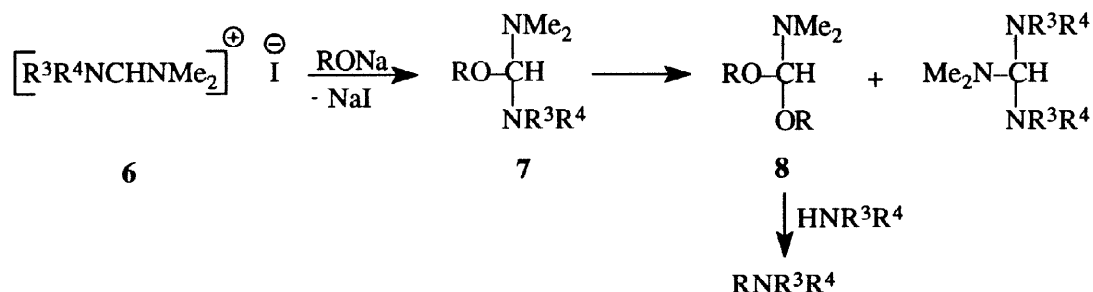
In a control experiment the Murahashi reagent **1** was caused to react with excess dimethylamine in DMF. After 15 - 20 h at 90° the reaction afforded after work-up a quantitative yield of methylaniline. When the reaction was performed under identical conditions without any dimethylamine added to the reaction mixture, no reaction ensued. Even prolonged heating at higher temperature (120°, 24 h) with and without catalyst (*N*-methyl-*N*-phenylammonium bromide) added, failed to produce any changes in **1** detectable by ¹H or ¹³C NMR spectroscopy.

Thus it is indicated that the added, more nucleophilic amine, is effecting exchange of the amino group in the Murahashi reagent, and that the reaction when performed in DMF proceeds via the modified reagent **5**. The reagent in question, *N,N*-dimethylaminotriphenylphosphonium iodide, can not be isolated under the abovementioned conditions since it reacts immediately with DMF (see below).

In order to shed further light on the reaction mechanism we prepared the bromine analog of **5** in a separate synthesis. We opted for the bromide rather than the iodide, as this made for an easier synthetic route and the anion presumably does not influence the reactivity of **5**. Reaction of a solution of triphenylphosphine with tetrabromomethane in the presence of an excess of dimethylamine at room temperature gave *N,N*-dimethylaminotriphenylphosphonium bromide as a stable, crystalline product, m.p. 237°. When heated in a NMR tube with DMF-*d*₇ as solvent, this analog of **5** afforded after 2 h at 112° a quantitative yield of **6** ($\text{R}^3 = \text{R}^4 = \text{Me}$). The progress of the reaction was followed with ¹H and ¹³C NMR and the clean conversion of **5** into **6** and triphenylphosphine oxide was observed intermittently until the reaction was completed.

When formamidinium salts react with alkoxides, aminalesters **7** are produced as already shown in 1967 by Bredereck et al. [9]. Aminalesters rearrange easily to the corresponding, somewhat less reactive [10] amidacetals [9, 10] **8** which are known [11] to react even with very weak amino nucleophiles, *i.e.*, imines to yield the corresponding alkyimines.

By analogy, the present reagents lead to amines via the following reaction path:



Thus, it has been established that alcohols ROH can be converted to amines RNR^3R^4 by the action of HNR^3R^4 and **1**, but only under forcing conditions and not via the intermediate **2** as suggested [5].

Our present observations are supported by the fact that despite numerous references to the Tanigawa reaction [5] in reviews and textbooks, there has been no report by any worker in the field that has actually made any amine by this particular method since the work was published in 1975.

In view of the high temperature/long reaction times needed to bring about the Tanigawa amination, it was of interest to improve the synthesis, specifically by introducing the essential intermediate **5** in a more efficient way, avoiding drawbacks such as strong bases, high temperature and expensive reagents like **1**.

Our main interest focused upon the $\text{Ph}_3\text{P}/\text{CCl}_4$ system. Despite one early report [12] detailing the preparation of aziridines from 2-amino alcohols, its potential use for the preparation of amines has not been explored. This is rather surprising in view of the simplicity and mild conditions of the method and might indicate that efforts in this direction has met with difficulties.

Regardless of these initial misgivings, we made an attempt to extend the $\text{Ph}_3\text{P}/\text{CCl}_4$ methodology to ordinary amines. Thus, in an initial experiment we mixed triphenylphosphine (5 mmol), with benzyl alcohol (5 mmol) in acetonitrile (6 ml), added diethylamine (10 mmol) followed by tetrachloromethane (1.5 equivalents). The temperature of the reaction mixture rose briefly to about 35° after 5 - 10 min.

The reaction mixture was thereafter heated at reflux for 1 h. Subsequent addition of water followed by dilute HCl/NaOH treatments and extraction into pentane yielded after drying (MgSO_4) the expected product, *N*-benzyl-*N,N*-diethylamine, as a colourless, virtually pure oil in about 84 % yield.

Under the same experimental conditions piperonyl alcohol was transformed cleanly into *N*-diethyl-*N*-piperonylamine. In this case the acid/base treatment was omitted, however. The amine was purified by flash chromatography on Merck No. 9385 silica gel 60, using ethyl acetate/hexane as eluent. Yield: 75%.

Contrary to the experience with 2-amino alcohols, where good to excellent yields of the corresponding aziridines are obtained at or below room temperature [12] the present amination is too slow to be of much value when performed under the abovementioned mild conditions [12]. Benzyl alcohol, for example, afforded only about 32 % yield of *N*-benzyl-*N,N*-dimethylamine when allowed to react with $\text{Ph}_3\text{P}/\text{CCl}_4$ and excess dimethylamine for 64 h at room temperature.

References

- [1] March J. *Advanced Organic Chemistry*. New York: Wiley. 1992: 414.
- [2] Mitsunobu O. In: Trost BM, Editor. *Comprehensive Organic Synthesis*. Vol. 6. New York: Pergamon Press. 1991: 65-101.
- [3] Dharmapal SD, Kozikowski AP. *Tetrahedron Lett.* 1994; 35: 977- 980.
- [4] Castro B, Selve C. *Bull. Soc. Chim. Fr.* 1971: 4368-4373.
- [5] Tanigawa Y, Murahashi S.-L, Moritani I. *Tetrahedron. Lett.* 1975; 16: 471-472.
- [6] Okada I, Ichimura K, Sudo R. *Bull. Chem. Soc. Japan.* 1970; 43: 1185-1189.
- [7] Hendrickson JB, Hussoin MS. *Synlett* 1990: 423-424.
- [8] Frøyen P, Juvvik P. *Tetrahedron Lett.* 1995; 36: 9555-9558.
- [9] Bredereck H, Simchen G, Hoffmann H, Horn P, Wahl R. *Angew. Chem.* 1967; 79:311.
- [10] Kantlehner W. J. *Pract. Chem.* 1995; 337: 418-421.
- [11] Philips KD, Horwitz JP. *J. Org. Chem.* 1975;40: 1856-1858.
- [12] Appel R, Kleinstück R, Ziehn KD, Knoll F. *Chem. Ber.* 1970; 103: 3631-3639.