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A convenient method for the preparation of primary amines using tritylamine

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This article is dedicated to the memory of Ifig. Photaki, Professor of Organic Chemistry, University of Athens, for her scientific contributions to peptide science

Abstract—A simple method for the preparation of primary amines by treating *N*-tritylamines with trifluoroacetic acid has been established. The *N*-tritylamines were prepared by the reaction of alkyl halides or alkyl *p*-toluenesulfonates with tritylamine, or by the reaction of alkyl bromides with lithium tritylamide.

1. Introduction

Primary amines are very important in human life and the chemical industry. Numerous important methods for the synthesis of primary amines have been described, including alkylation of ammonia,[1] reductive amination of carbonyl compounds,[2] reduction of azides and of amides.[3] Alkylation of protected ammonia,[4] as an ammonia synthon, by alkyl halides or alkyl tosylates is one of the most useful methods for the preparation of primary amino compounds. Potassium phthalimide, hexamethylenetetramine, guanidine, sodium diphenylphosphinamide, bisarylsulfenimides, silyl derivatives of amines and sodium diformylamide are among the ammonia synthons[4] reported to react with alkylating agents to give, after deprotection, primary amines. Moreover, polymer-bound ammonia equivalents were introduced[5] to afford primary amines, after suitable cleavage. Most of these methods are versatile reactions and afford good yields, but often the primary amines obtained are contaminated[1] with secondary and tertiary amines and the workups require laborious purifications. Yields are not always satisfactory with ammonia synthons, due to their relatively poor nucleophilicity, which may lead to elimination products.[4] In addition, many of the above procedures cannot be applied in the presence of certain functional groups, which react under the reaction conditions.

In the search for a mild, simple and convenient method for the conversion of alkyl halides, alcohols or their derivatives to the corresponding primary amines, the application of triphenylmethylamine (tritylamine) was examined as an alternative reagent, with the consideration that the trityl–nitrogen bond is easily cleaved by acid. The trityl moiety is a valuable acid-labile bulky protective group for peptide, carbohydrate and nucleotide chemistry, readily introduced as a cation at a nucleophilic site, mostly in the form of trityl chloride. It can be cleaved selectively even in the presence of other acid sensitive protecting groups.[6] The extremely mild conditions, under which the *N*-trityl group can be removed, and the benefits of monoalkylation, make tritylamine a very useful aminating agent in organic synthesis. Furthermore, most of the *N*-tritylamino compounds obtained in the reaction mixture, are crystalline solids and can be easily separated and purified by recrystallization, due to the

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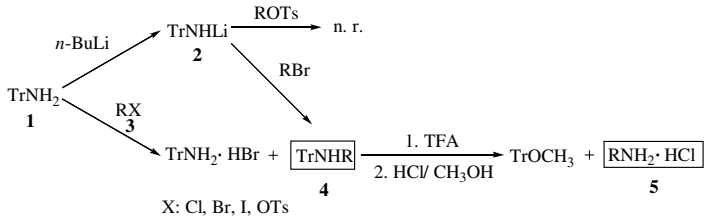


Scheme 1. General reaction pathway.

high symmetry of the crowded trityl group. However, despite the wide use of the *N*-trityl moiety, only few references have been reported on the applications of tritylamine in organic synthesis.[7–9]

In the present work, a simple and mild method for the synthesis of primary amines is described, including the amination of alkyl halides and alkyl tosylates by the use of tritylamine, as an ammonia synthon, and the subsequent detritylation with trifluoroacetic acid at room temperature. The synthetic route is outlined in Scheme 1.

2. Results and discussion

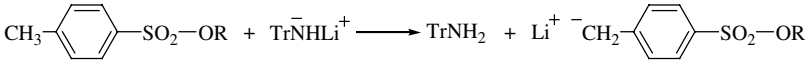
Primary alkyl bromides and iodides react smoothly in acetonitrile with tritylamine $TrNH_2$ (**1**), behaving both as a base and as the aminating agent, to give *N*-tritylamines TrNHR **4** and the salt of $TrNH_2$·HBr, which is removed by filtration and recycled. *n*-Alkyl chlorides react very slowly. Chain extension or branching of the alkyl group reduces the reactivity of the halide, which must be used in excess in order to increase the reaction rate. The reaction is more sluggish with secondary halides, and fails with tertiary halides. Allylic, propargylic and benzylic halides react faster than the alkyl ones and give almost pure crystalline TrNHR, which are detritylated much easier than the alkyl derivatives. Alkyl tosylates[10] ROTs react faster in refluxing toluene, than in acetonitrile, in the presence of triethylamine, which reduces the reaction time, giving the desired TrNHR **4**.

The TrNHR can also be prepared from alkyl bromides and lithium tritylamide (**2**), formed by the reaction of $TrNH_2$ and *n*-BuLi in THF (Scheme 1). Alkyl tosylates do not react with the tritylamide to obtain TrNHR, possibly because tritylamide, as a strong base, abstracts an acidic proton from the *p*-methyl group of the tosyl ester to give a stabilized benzylic anion[11] (Eq. 1).

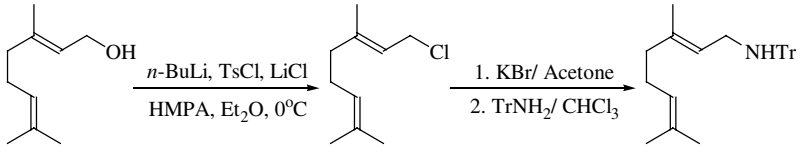
Deprotection of TrNHR was achieved very simply, after treatment with TFA for a few minutes or after refluxing with 1 N HCl in MeOH for some hours. The trityl cation was removed as TrOMe, while the hydrochloride salts of the primary amines RNH_2·HCl **5** were obtained after vacuum distillation of TFA and subsequent treatment of the residue with HCl in CH_3OH, followed by dry ether.

This method was applied for the amination of geranyl chloride, which was prepared from geraniol, with minor modifications of the reported procedure[12] and without further purification. Although geranyl chloride failed to react with $TrNH_2$, *N*-geranyl tritylamine (TrNHGer)[13] was obtained easily in the presence of KBr in acetone, after a halogen exchange reaction (Eq. 2), in high yield (Table 1).

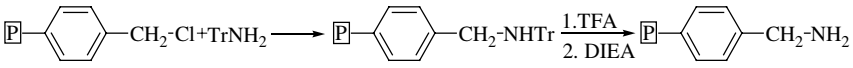
It is worthy to note that this amination reaction was also applied to the preparation of cross-linked polymeric amines from the corresponding chloromethylated resins (Eq. 3), which are useful supporting materials, especially for peptide synthesis. The results of the present work are summarized in Table 1.



(1)



(2)



(3)

Table 1. Synthesis of primary amine HCl salts

Entry	Reagent	$TrNH_2$/RX	RX	Time, temp	TrNHR yield% (mp °C)	RNH_2·HCl (mp °C)[a]
1	**1**	1:5	CH_3I	1 day, rt	90 (93–94)	227–9 (227–8)[4j]
2	**1**	1:5	C_2H_5Br/I	2–5 days, rt	92 (78–9)	107–9 (96[4h], 79-81[4e])
3	**1**	1:10	*n*-C_4H_9Br	10 days, rt (or 2 days, 40 °C)	88 (oily)	194–5 (194[4e])
4	**1**	1:2	*n*-C_4H_9OTs	5 h, reflux	90 (oily)	See entry 3
5	**1**	1:2	*iso*-C_4H_9OTs	8 h, reflux	70 (oily)	167–9 (168–71[3b])
6	**1**	1:10	*n*-$C_5H_{11}Br$	12 days, rt	85 (oily)	215–7 (217–8[3c])
7	**1**	1:10	*n*-$C_7H_{15}Br$	15 days, rt (or 3 days, 40 °C)	75 (oily)	234–7 (240[4d], 246[4h])
8	**1**	1:2	*n*-$C_7H_{15}OTs$	10 h, reflux	80 (oily)	See entry 7
9	**1**	1:2	$C_{12}H_{25}OTs$	15 h, reflux	78 (oily)	183–5 (185[4d])
10	**1**	1:5	CH_2=CH–CH_2Br/Cl	3 days, rt	>90 (83–4)	108–9 (106[4h], 104–9[4e])
11	**1**	2:1	Ger-Cl, KBr	2 h, 40 °C	>90 (oily)	118–20 (118[4h])
12	**1**	1:5	CH≡C–CH_2Br	3 days, rt	>90 (166)	178–9 (177–80[3b])
13	**1**	2:1	Ph–CH_2Br/Cl	1 day, rt	>90 (92–3)	243–4 (243–4[4e])
14	**1**	2:1	*p*-Br–$C_4H_4CH_2Br$	2 days, rt	>90 (143)	285–7 (281–3[15])
15	**1**	2:1	*p*-O_2N-$C_4H_4CH_2Br$	2 days, rt	>90 (168)	255–7(258–60[3c])
16	**1**	4:1	**P**-$C_6H_4CH_2Cl$	3–4 days, 40 °C	>90	
17	**2**	1:2	*n*-C_4H_9Br	−15–0 °C, 1 h, then 4 h, rt	65 (oily)	See entry 3
18	**2**	1:2	*n*-$C_7H_{15}Br$	−15–0 °C, 1 h, then 4 h, rt	62 (oily)	See entry 7
19	**2**	1:2	ROTs (R: alkyl)	−15–0 °C, 1 h, then 4 h, rt	No reaction	

[a] Literature melting points are given in parentheses.

In summary, we describe a simple, mild and convenient method for the synthesis of primary amines, in the form of HCl salts, from the corresponding alkyl, allyl, propargyl and benzylic halides or alkyl tosylates and the ammonia equivalent, tritylamine, in high overall yields, after mild detritylation of the initially formed *N*-tritylamines with trifluoroacetic acid. This procedure is environmentally friendly and economic, the starting materials are readily available and the by-products produced can be easily separated and recycled. We are currently exploring the preparation of primary amides using tritylamine.

3. Typical experimental procedure

3.1. Synthesis of TrNHR (4)

(a) To a solution of 1 mmol tritylamine[14] in 5 ml of CH_3CN 1–10 mmol RBr were added and the resulting solution was either left at rt for several days or refluxed for several hours (see Table 1). The precipitated salt $TrNH_2$·HBr was removed by filtration and recycled, and the solvent was concentrated in vacuo. The residue was purified by recrystallization from ethanol, or by column chromatography (ether/petroleum ether). Total yield: 70–93% of TrNHR. (b) A solution of 5 mmol $TrNH_2$, 10 mmol Et_3N and 5–10 mmol ROTs in 5 ml of toluene was refluxed for 5–15 h. The precipitate was removed and the organic layer, after water extraction, was concentrated in vacuo. The residue was purified by column chromatography Yield: 70–90% of TrNHR. (c) To a stirred solution of 5 mmol of $TrNH_2$ in abs. THF, cooled to −15–0 °C, 5 mmol of *n*-BuLi in hexane were added dropwise under N_2. After 30 min, 10 mmol of RBr in 5 ml THF were added, and the stirring was continued for about 2 h at −10 to 0 °C and about 4–5 h at rt. The reaction was quenched with water at 0 °C under N_2 and the product was extracted with ether and purified as above. Yield: 60% of TrNHR. All the TrNHR's in the Table 1 were identified by IR and ^{1}H NMR spectroscopy and by elementary analysis.

3.2. Detritylation/RNH_2·HCl (5)

TrNHR (1 mmol) in a solution of 5 ml 60% TFA in CH_2Cl_2 was stirred for 10 min at rt, then 2 ml of CH_3OH were added and the yellow colour immediately disappeared. After stirring for about 1 h, the solvent was evaporated in vacuo and the hydrochloride salt RNH_2·HCl was precipitated by the addition of 10 ml 1 N HCl in CH_3OH and subsequent concentration to dryness. The salt was washed with dry ether.

3.3. Preparation of cross-linked polymeric amines

One millimole of 1% cross linked Merrifield resin and 1.04 g (4 mmol) of $TrNH_2$ were suspended in a solution of 20 ml of 30% DMF/CH_2Cl_2 and the mixture was warmed to 40 °C for 3 days, then cooled to rt, filtered and washed thoroughly with DMF, MeOH, CH_2Cl_2. The detritylation was effected by treating with 40% TFA/CH_2Cl_2 for 15 min, then adding 5 ml of CH_3OH and stirring for further 10 min, filtering, and washing with CH_2Cl_2, 10% DIEA/CH_2Cl_2, CH_2Cl_2, MeOH, CH_2Cl_2.

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13. TrNHGer: IR (3330, 1651 cm^{-1}) ^1H NMR ($CDCl_3$, 200 MHz) δ 1.59 (s, 3H, CH_3),1.81 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.22 (m, 4H, CH_2CH_2), 2.95 (d, 2H, CH_2N), 5.31 (m, 1H, $CH{=}CMe_2$), 5.55 (m, 1H, $CH{=}CH_2N$), 7.35–7.55 (m, 9H, Ar-*H*), 7.74 (d, 6H, Ar-*H*).
14. Tritylamine was prepared by stirring vigorously TrCl with an excess of 25% ammonia solution in CH_2Cl_2 for 2 days, followed by the suitable treatment: the organic layer was concentrated to dryness, diluted with Et_2O, HCl (g) was bubbled into, and the precipitated hydrochloride salt was filtered, washed with Et_2O, treated with 50% NaOH under cooling and extracted with Et_2O. The tritylamine obtained was purified by recrystallization from EtOH. Yield 70%, mp 102 °C, reported: 102–103.5 °C, Mandell, L.; Piper, J. U.; Pesterfield, C. E. *J. Org. Chem.* **1963**, *28*, 574–575.
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