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Strategies for protecting and manipulating triazine derivatives

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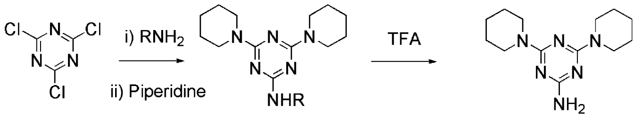
Abstract—Aminotriazine derivatives are available in two steps by treating chlorotriazines with acid-labile benzylic amines including triphenylmethylamine, diphenylmethylamine, and 2,4-dimethoxybenzyl-amine (Dmb-amine), followed by deprotection using trifluoroacetic acid. This high yielding (85–99%) protocol is a milder alternative to the traditional method that uses ammonia and high temperature as a route to aminotriazine derivatives. The nucleophilic substitution reaction that installs the benzylic amine on monochlorotriazine herbicide derivatives may be performed using conventional heating. Alternatively, a microwave reactor can be used to decrease the reaction times 100-fold. The intermediates in these syntheses are soluble in a range of organic solvents and amenable to chromatography. In some cases when dimethoxybenzyl groups are used, oligomerization of the dimethoxybenzyl side product upon treatment with trifluoroacetic acid yields a precipitate that facilitates purification by simple filtration.

Triazine chemistry has experienced a renaissance due to the utility of melamine derivatives as precursors of a variety of oligomers[1] or polymers,[2] as scavenging resins in organic manipulations,[3] as components of host–guest[4] and 'superstructure'[5] assemblies, as ligand scaffolds for catalysis,[6] and in medicinal chemistry.[7] The appeal of the *s*-triazine core is largely due to the ease of systematic substitution of the chloride atoms with amine nucleophiles to generate a variety of structures. Consecutive substitution reactions with good nucleophiles such as primary or secondary amines proceed as a one-pot procedure: the first substitution occurs at low temperature; the second substitution occurs slower, but at ambient temperature; and the third substitution typically requires temperatures above 80 °C.

Many of these targets possess an NH_2-group on the triazine ring. Most syntheses of NH_2-substituted triazines continue to use the original procedures developed by the American Cyanamide Co.[8] Wherein cyanuric chloride is reacted with ammonia at low temperature to yield amino-dichloro-*s*-triazine which in turn may be used to prepare other NH_2-substituted triazine derivatives. However, this compound's poor solubility and the more modest reactivity of this monosubstituted triazine toward other nucleophiles often makes installation of this NH_2-group more preferable as the last step. In such cases, installation of this NH_2-group requires more forcing conditions. Typically this involves ammonium hydroxide (or ammonia), temperatures that exceed 100 °C, extended periods of time, and specially designed glass bombs. Here, we describe an alternative simpler strategy to install this group at any point in the synthesis.

Benzylic groups such as the dimethoxybenzyl (Dmb) and trityl groups are widely used as acid-labile protecting groups for nitrogen substituents in synthesis. Examples of their utility are seen in syntheses of peptides,[9] amides,[10] 2-acetamide glycosyl donors,[11] amines,[12] and a variety of heterocycles such as 1,2,4-triazoles,[13] 1,2-thiazetidine 1,1-dioxides,[14] and maleimides.[15] Dmb and trityl groups have labile benzylic C–N bonds due to the stability of the intermediate benzylic carbocation. Here we describe the utility of these benzylic amines, RNH_2 in aminotriazine synthesis (Scheme 1). Here we describe the utility of a two step sequence to yield



Scheme 1. Synthesis of triazine derivatives using the benzylic amines (RNH_2) identified in Table 1.

Keywords: Triazine; Protecting group.

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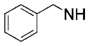
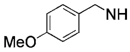
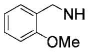
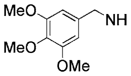
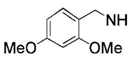
aminotriazines: reaction with suitable benzylic amines followed by mild acid-catalyzed deprotection. Scheme 1 shows the synthesis of the benzyl derivatives.

Table 1 reports the yield for the preparation of the desired model compounds and the results of their treatment with trifluoroacetic acid (TFA). Cleavage to generate the desired 2,4-dipiperidinyl-6-amino-*s*-triazine occurs only when triphenylmethylamine (tritylamine), diphenylmethyl-amine, or 2,4-dimethoxybenzylamine (Dmb-amine) were incorporated (**5**–**7**). As expected, the ease of cleavage correlated with the presumed stability of the intermediate carbocation. When a trityl cation was generated from **7**, the product formed in less than 5 min as indicated by a bright yellow solution. Generation of the deeply green diphenylmethyl cation from **6** took approximately 16 h. Cleavage of the Dmb group from **5** to produce a violet solution requires 2 h. In this example, the cleaved Dmb group underwent oligomerization,[16] and as a result, chromatography was not required to separate the aminotriazine products from the Dmb products. Instead, purification was achieved by simple filtration.

Introducing the NH_2-group last is the least attractive route to aminotriazine derivatives as it requires the harsher conditions of the American Cyanamide procedure. Scheme 2 illustrates the utility of the reaction of Dmb-amine with monochlorotriazines using two triazine herbicides, atrazine (**8**) and turbutazine (**9**).

Substitution of **8** or **9** with Dmb-amine proceeds in acceptable yields using conventional methods (Table 2) although the reaction times are long and vary only slightly with solvent choice. Dimethylacetamide (DMA) afforded product after 12 h of heating. The time required for complete conversion to the product varied with the solvent employed. Dimethylacetamide (DMA) was the solvent of choice, affording product after only 12 h of heating. Other solvents such as THF, *p*-dioxane, or ethanol required several days to completely convert the monochlorotriazine herbicide to a Dmb-amine derivative. However, a microwave reactor permitted quantitative formation of the herbicide-containing product in 5–15 min. This 100-fold decrease in reaction time greatly facilitates this chemistry and represents one of the first examples where this technology has been used in aminotriazine synthesis. Microwave techniques have become increasingly prevalent in literature.[17] They have also been used to prepare triazine derivatives; however, in most cases this only involves assembly of the triazine core.[18] In this case, microwave technology enhances nucleophilic aromatic substitution of the monochlorotriazine.[19]

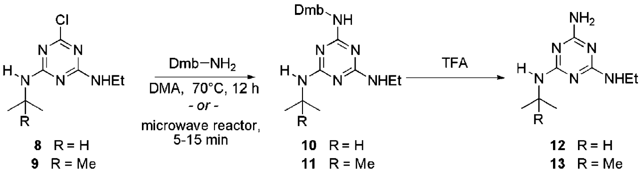
Table 1. Yields of intermediates, cleavage times, and products

Compd	R	Isolated yield/%	Cleavage time[a]	Yields observed (isolated)/%
1		73	12 h	0[b] (83)
2		99	12 h	0[b] (87)
3		96	12 h	0[b] (80)
4		84	12 h	0[b] (87)
5		91	2 h 1 h	>99 (93) 70
6	Ph_2HC–NH	85	16 h	99 (63)[c]
7	Ph_3C–NH	85	5 min	99 (93)

[a] Refers to time required to affect the TFA cleavage.

[b] No cleavage of the benzylic amine was observed; rather, the TFA salt was isolated and characterized.

[c] Although cleavage of the C–N bond appears to be quantitative as monitored by ^{1}H NMR spectroscopy, the isolated yield of this product is low due to the formation of additional (unidentified) by-products.



Scheme 2. Preparation and manipulation of the benzylic amine derivatives of herbicides.

Table 2. Optimization of the synthetic protocol to generate the biologically relevant triazine derivatives suitable for treatment with TFA

Compd	Solvent	Temperature/°C	Time	Isolated yield/%
8	*p*-Dioxane	80	2 d	94
8	EtOH	70	3 d	70
8	DMA	70	12 h	99
8	*p*-Dioxane	150	10 min[a]	98
8	EtOH	150	5 min[a]	99
8	DMA	80	5 min[a]	99
9	*p*-Dioxane	150	2 d	86
9	*p*-Dioxane	150	15 min[a]	97
9	EtOH	150	10 min[a]	84
9	DMA	150	10 min[a]	77

[a] Microwave experiments.

Successful installation of the Dmb-amine group on monochlorotriazines led us to reexamine the use of trityl amine. While our efforts demonstrated that cleavage of the trityl group from a triazine derivative is more facile than cleavage of the Dmb-amine, substitution of the third chlorine atom of atrazine with tritylamine was unsuccessful even with heating at 120 °C in *p*-dioxane for 2 weeks. Reaction of atrazine with tritylamine in DMA also failed to produce desired product using microwave techniques (20 min at a temperature of 150 °C).

Removal of the Dmb group from **10** and **11** with TFA afforded near-quantitative cleavage of the Dmb group in 12 h. In these cases, chromatography was necessary