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Tritylamine as an Ammonia Surrogate in the Ugi Tetrazole Synthesis

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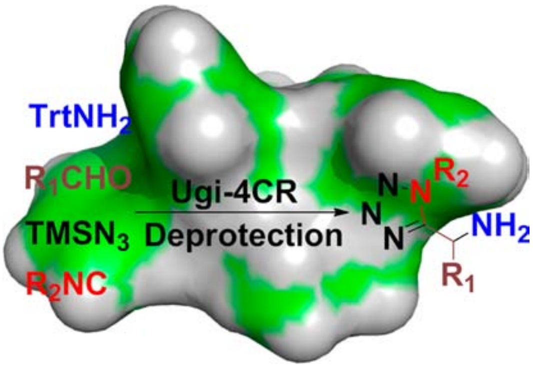
ABSTRACT



The role of tritylamine is introduced as a convenient ammonia substitute in the Ugi tetrazole synthesis. Fifteen examples and their mild cleavage products are described in satisfactory to good yields. *N*-Unsubstituted α-aminotetrazoles are important compounds with annotated biological activities, and the described two-step synthesis provided an alternative route to otherwise difficult to access derivatives.

The Ugi reaction is well-known for its very broad scope of different starting materials.[1] Thousands of reported examples revealed that most primary or secondary amines, aldehydes, ketones, and isocyanides could react with a suitable acid component.[2−15] However, ammonia is one of the very few amine components which gives regularly unsatisfactory results in Ugi-type multicomponent reactions for many potential reasons. First, ammonia is a very reactive amine, and the Schiff bases of ammonia are known to be unstable and to rapidly cyclo-trimerize or oligomerize. The Schiff base is a key intermediate in all Ugi-type multicomponent reactions (MCRs).[16−19] The slow kinetic reversibility of the Schiff base oligomer monomer equilibrium could hinder the progress of the Ugi MCR and also potentially lead to side reactions. The high basicity

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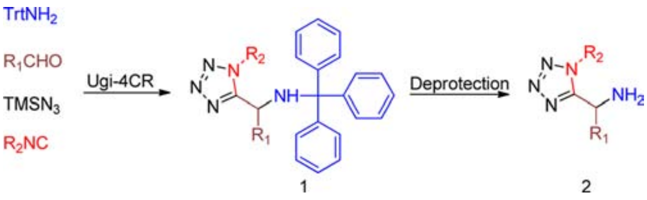
of ammonia used in excess could suppress Lewis and Brønsted acid mediated activation of the intermediate Schiff base. In the tetrazole and Ugi-3CR variation the Schiff base causes a primary amine to be formed from use of ammonia. This primary amine, however, is very reactive and can undergo an additional Ugi reaction; with highly reactive oxo components, e.g., formaldehyde, even a third Ugi reaction can even lead to a mixture of multiple products. In fact, the HPLC−MS analysis of the reaction of *tert*-butyl isocyanide with formaldehyde, ammonia, and TMS-azide revealed such a mixture of mono-, di-, and tri-Ugi products. While several ammonia substitutes such as ammonium formiate,[20] ferrocenylalkylamines,[21] substituted benzylamines,[22] and anomeric glycosylamines[23] have been described in the past for the Ugi-4CR, no conveniently and mildly cleavable substitutes were known for the Ugi tetrazole synthesis.[24,25] N-Unsubstituted α-aminotetrazoles, however, are potentially biologically active compounds with currently no described synthetic pathway. Therefore, we report our results introducing tritylamine as a convenient ammonia surrogate in the Ugi tetrazole synthesis (Scheme 1).

Scheme 1. Design of a Synthetic Pathway to N-Unsubstituted Primary α-Aminotetrazole Using a Ugi-4CR Employing Tritylamine as an Ammonia Surrogate



At the beginning of our investigations, it was not clear that tritylamine, although a well-known amine protecting group often used in peptide chemistry, might work well in the crucial Schiff base formation due to sterical hindrance. We were pleased to find the expected product during the room temperature reaction of cyclohexylisocyanide, isobutyraldehyde, tritylamine, and TMS-azide in methanol, however, accompanied with mostly starting materials indicated the low conversion. Switching to microwave conditions (100 °C, 30 min, ethanol) has led to good conversion and isolation of the Ugi product in satisfactory yields (**1i**, 70%). In order to find out the rate-limiting step (Schiff base formation or α-addition and subsequent tetrazole formation), we attempted to run both reactions at room temperature. It was found that the Schiff base formation was too slow at room temperature but successful if performed under microwave conditions. Interestingly, we found when we mixed the isolated Schiff base with the isocyanide and $TMSN_3$ (ethanol, 24 h) the reaction yielded *N*-trityl-protected α-aminotetrazoles (**1d**, 55%) in even slightly higher yields than that of microwave condition (**1d**, 47%). It was concluded that the microwave or thermal conditions must be employed for the Schiff base formation of tritylamine but not for the subsequent Ugi reaction. For the sake of a convenient procedure, however, all subsequent reactions were performed in the microwave in a one-pot fashion. In order to test the scope and limitations of the reaction, several isocyanides and aldehydes were tested (Scheme 1, Table 1). Cyclohexanone, which previously has been described in the literature as a good substrate for diverse Ugi reactions, was reacted; however, the expected product could not be isolated. This is presumably due to the high sterical hindrance of the two reactants, and not surprisingly, no such Schiff base with tritylamine has been reported with a ketone via a condensation reaction.

Table 1. Yields of *N*-Trityl-Protected α-Aminotetrazoles (**1**) and *N*-Deprotected α-Aminotetrazoles (**2**)

no.	R_1	R_2	yield of **1** (%)	yield of **2** (%)
a	H_2	$C_6H_5(CH_2)_2$	83	99
b	CH_3	$C_6H_5(CH_2)_2$	80	99
c	$(CH_3)_2CH$	$C_6H_5(CH_2)_2$	76	99
d	$CH_3S(CH_2)_2$	$C_6H_5CH_2$	47	99
e	$(CH_3)_2CHCH_2$	$C_6H_5CH_2$	87	86
f	cyclopropionyl	$C_6H_5CH_2$	73	99
g	CH_3	cyclohexyl	81	98
h	isopentyl	$C_6H_5CH_2$	66	99
i	$(CH_3)_2CH$	cyclohexyl	70	99
g	$C_6H_5CH_2$	cyclohexyl	41	99
k	cyclohexyl	cyclohexyl	87	99
l	$C_6H_5(CH_2)_2$	cyclohexyl	75	99
m	$CH_3OCO(CH_2)_2$	$C_6H_5(CH_2)_2$	65	99
n	$CH_3CH_2OCOC_3H_4$	$C_6H_5(CH_2)_2$	77	99
o	$CH_3CH_2OCOC_3H_4$	$(CH_3)_3$	46	98

The deprotection of the Ugi intermediates could be performed under standard conditions (DCM, TFA, rt, 1 min). The products were isolated by chromatography in near-quantitative yields (Table 1).

It was widely accepted that the mechanism of the Ugi reaction involves first Schiff base formation (or enamine in the case of secondary amines), followed by an activation step of the imine by a Lewis or Brønsted acid. Addition of the isocyanide via the carbon onto the Schiff base yields an intermediate nitrilium ion, addition of the acid, and a final irreversible sigmatropic rearrangement to the product, a tetrazole in the present case (Scheme 2).

This mechanistic proposal has been recently also supported by theoretically high-level molecular orbital calculations.[26]

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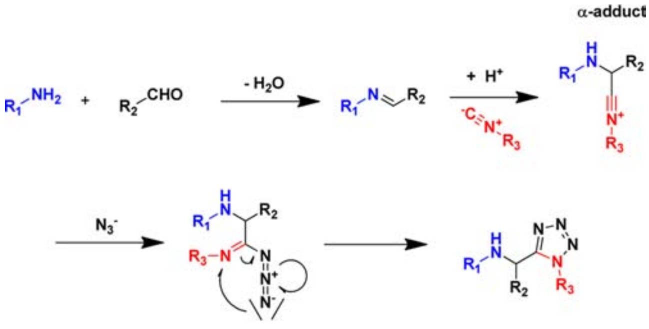
Scheme 2. Ugi Tetrazole Mechanism



The present Ugi reaction was, however, surprising in several respects. First, the reactive imine carbon next to the tritylamine unit is sterically very hindered and reacts with the bulky isocyanide to give the nitrilium species. Then the azide anion has to add onto this species to yield the α-adduct. To underscore the bulkiness of this intermediate a molecular modeling picture of the presumed intermediate of product **2k** is depicted in Figure 1.[26] After the ring closure, the α-amino tetrazole is formed. The compounds generally crystallized well, and two typical highly crowded examples are shown in Figure 2 in the solid state. After trityl deprotection, the primary amines are obtained as TFA salts which also nicely crystallized (Figure 2).

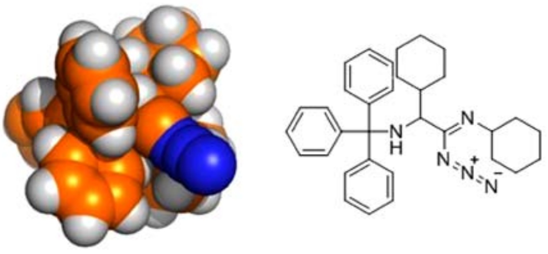


Figure 1. Spheres model of the α-adduct during the formation of tetrazole **2k** illustrating the crowdedness of the reaction intermediate.

N-Tetrazole-substituted and amino-*N*-unsubstituted α-amino tetrazoles so far have been only synthesized via the Ugi reaction.[25] We have now introduced tritylamine as a convenient and easily cleavable ammonia surrogate that reacts together with aldehydes, TMS-azide, and isocyanides to yield *N*-trityl α-aminotetrazoles. The *N*-unsubstituted α-aminotetrazoles were obtained under very mild and standard trityl deprotecting conditions. Despite steric hindrance, the Ugi reaction proceeded smoothly and the products could be isolated in good to satisfactory yields. Work is ongoing to investigate the further synthetic applications and biological properties of the new compounds.

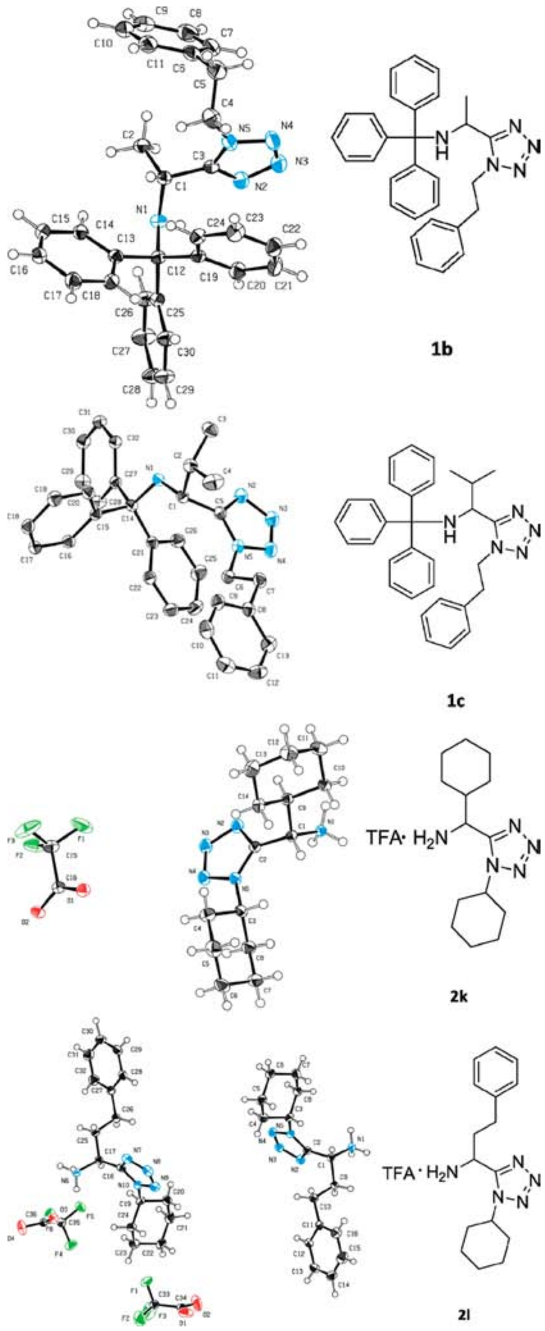


Figure 2. Molecular structures of **1b** and **1c** in the solid state illustrating the crowdedness of the trityl-protected products. Molecular structure of trityl-cleaved products **2k** and **2l** in the solid state. ORTEP ellipsoids drawn at the 50% probability level.

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Supporting Information Available. Experimental procedures, compound characterization, spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.