Tetrahedron Letters, Vol.31, No.15, pp 2109-2112, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

AMINO PROTECTION USING TRIAZONES

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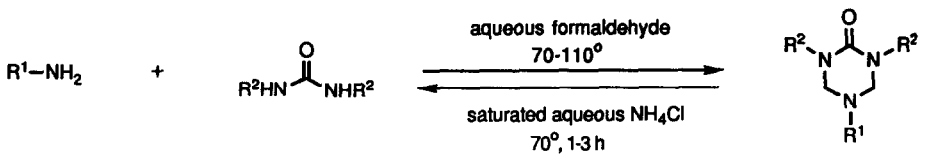
Summary: *Primary amines protected by incorporation into a "triazone" derivative (3) are stable to various reduction, oxidation, organometallic, and basic hydrolysis conditions, and may be regenerated by treatment with aqueous ammonium chloride at 70°. An application to polyamine synthesis is described.*

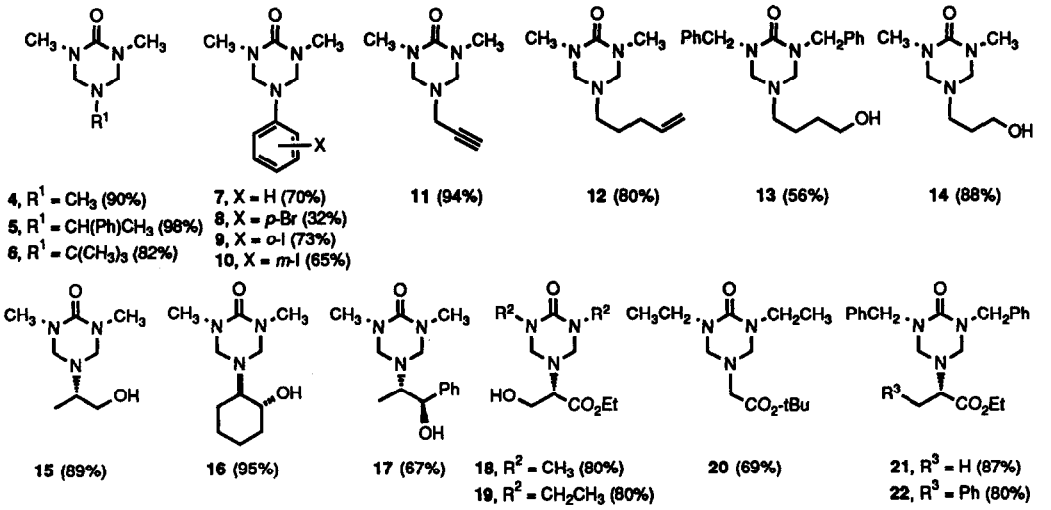
Temporary amino protection is typically achievable using a carbamate derivative, such as benzyloxycarbonyl (Z) or *t*-butoxycarbonyl (BOC), or an N-trityl, N,N-dibenzyl, N,N-disilyl, or N-phthaloyl derivative.[1,2] There is nonetheless a continuing need for amino protecting groups that have favorable formation and removal features, and that can withstand basic, nucleophilic, oxidative, reductive, and alkylation conditions that might arise during amino alcohol, polyamine, and peptide synthesis. We sought a new protecting group that blocks both N-H positions and does not contain an electrophilic carbonyl group or a nucleophilic nitrogen. The 1,3,5-tri-*N*-substituted hexahydro-2-oxo-1,3,5-triazine ("triazone") group (**3**), known for many years in other contexts,[3,4] appeared to have the required characteristics.



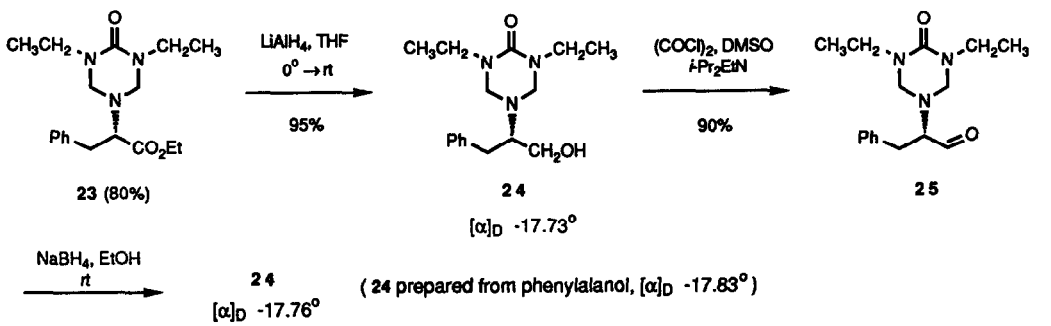
1 **2** **3**

Triazones **3** can be conveniently and inexpensively prepared from a primary amine **1** (1 equiv), aqueous formaldehyde (2–30 equiv), and a symmetrically disubstituted urea **2** (1 equiv).[3,5] Under these conditions, occasionally modified by the use of a cosolvent such as dioxane, ethanol, or toluene, the triazones **4** - **23** were assembled in the yields shown. In general, alkyl- and arylamines, unsaturated amines, amino alcohols, and (*S*)-α-amino esters form triazone derivatives. Additionally, triazone esters such as **21** may be hydrolyzed in high yield using ethanolic LiOH at room temperature to afford the triazone carboxylic acid. The products **3** may be chromatographed on silica gel without decomposition, although for many of them a simple extractive workup provides material of adequate purity. Methyl and benzyl have proven to be the most useful urea substituents, the former giving the highest yields and the latter exhibiting the most favorable solubility characteristics. N,N'-dicyclohexyl- and N,N'-diphenylurea gave poor yields of **3**.

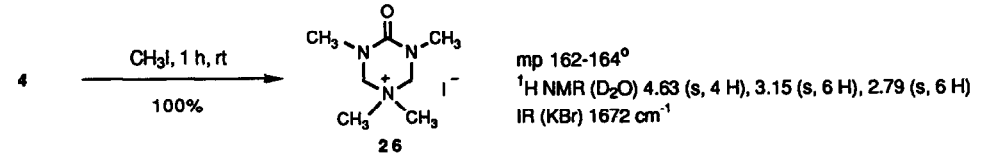
Triazone formation may occur by attack of the urea nitrogen on the formaldehyde iminium ion derived from the amine nitrogen.[6-8] Hydrolysis of **3** back to **1** could also involve iminium intermediates, be catalyzed by protonation on the carbonyl oxygen, and be driven by removal of formaldehyde. When triazones **3** were treated with saturated ammonium chloride (pH ~ 5) at 70°, hydrolysis to the amines **1** occurred after 1-3 h (for example, phenethylamine from **5**, 90% yield; 3-aminopropanol from **14**, 84%; trans 2-aminocyclohexanol from **16**, 92%; *t*-butylamine from **6**, 87%). The urea **2** is regenerated, and the formaldehyde is presumably consumed by reaction with ammonia.[9] These conditions are mild enough that other common amino protecting groups (BOC, Z, phthaloyl) are unaffected, as demonstrated by control experiments.



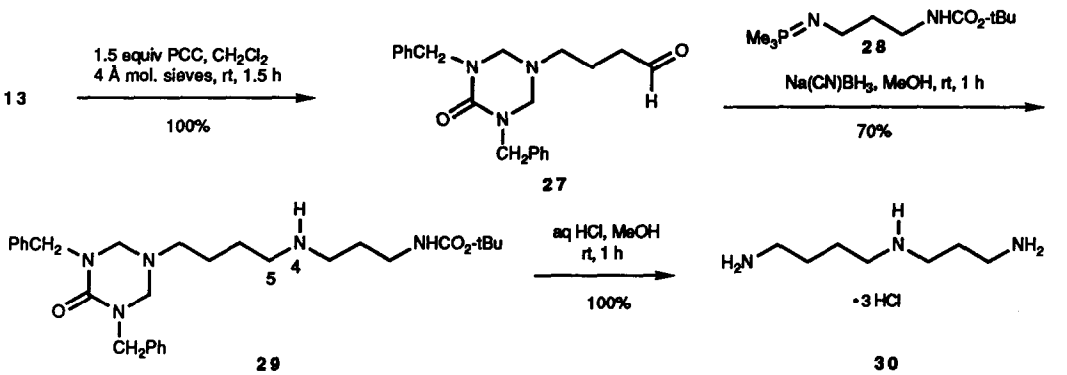
To investigate the configurational stability of triazones of α-amino esters and aldehydes,[10] the phenylalanine ethyl ester triazone **23** was reduced to the alcohol **24**, then oxidized to the aldehyde **25**. Reduction back to **24** gave material of nearly identical optical rotation, as did direct triazone formation from phenylalanol. It thus appears likely that a variety of chemical transformations may be carried out on polyfunctional triazones without epimerization at sensitive centers or destruction of the protecting group.[11]



A feature of triazone chemistry which may bear on the mechanism of acidic hydrolysis is revealed by the reaction of the methylamine triazone **4** with neat iodomethane to give the ammonium salt **26**.[12] Although **4** does not survive aqueous HCl at room temperature, **26** is stable in aqueous solution, suggesting that protonation on the amine nitrogen is not generally sufficient to initiate cleavage of a triazone ring.



The suitability of triazones for use in polyamine synthesis[13] is demonstrated by the preparation of spermidine (**30**) from the 4-aminobutanol triazone **13**. Oxidation[14] of **13** gave the stable, protected aminobutyraldehyde **27**. Coupling[15] of **27** to form the spermidine 4,5-bond was carried out using the iminophosphorane **28**, which in turn is available by Staudinger reaction[16] of trimethylphosphine and BOC-protected 3-azidopropylamine. Thus **27** and **28** were combined in THF solution in the presence of activated 4 Å molecular sieves. After 45 min, the solution was concentrated, and dry methanol and solid $Na(CN)BH_3$ were added. Reduction of the imine was complete after 1 h, and the product **29** was isolated by silica gel chromatography using 20 : 1 dichloromethane / methanol as the eluant. Aqueous acid readily cleaved both the triazone and BOC groups, and following trituration with THF to remove dibenzylurea, pure spermidine tris(hydrochloride) **30** (free of formadehyde derived residues and identical with authentic material by ^1H and ^{13}C NMR analysis) was isolated in quantitative yield. A noteworthy feature of this approach to polyamine synthesis is the absence of interfering cyclization reactions during the oxidation and reductive amination steps.[17]



Illustrative Procedures for Triazone Formation: 5-[1-(*S*)-(1-Carbethoxy)ethyl]-1,3-dibenzyl-hexahydro-2-oxo-1,3,5-triazine (21). A mixture of 0.768 g (5 mmol) of *L*-alanine ethyl ester hydrochloride, 1.2 g (5 mmol) of N,N'-dibenzylurea, and 5.0 mL (67 mmol) of 37% aqueous formaldehyde was stirred at 40° in a 100 mL three neck round bottom flask equipped with internal thermometer and Dean-Stark trap. A solution of 1.1 mL (10 mmol) of *N*-methylmorpholine in 1 mL of dioxane and 40 mL of toluene was added and the temperature was raised to 85°, whereupon the solution became homogeneous. Over a 90 min period, 35 mL of distillate was collected in the trap and 15 mL of toluene was added to the reaction mixture, as the internal temperature rose from 90 to 110°. The reaction mixture was cooled and concentrated to a semi-solid residue. Chromatography on silica gel using 3 : 2 ethyl acetate / hexanes as the eluant afforded 1.65 g (87%) of the triazone **21** as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) 7.30 (app s, 10 H), 4.57 and 4.49 (AB q, 4 H, J = 14), 4.25 and 4.14 (AB q, 4 H, J = 13), 3.84 - 4.10 (m, 2 H), 3.54 (q, 1 H, J = 7), 1.15 (t, 3 H, J = 7), 0.99 (d, 3 H, J = 7); IR (film) 1741, 1644 cm^{-1}; $[a]_D$ -38.2° (c=1.5, $CHCl_3$).

5-[1-(*S*)-(1-Carbethoxy-2-hydroxy)ethyl]-1,3-diethyl-hexahydro-2-oxo-1,3,5-triazine (19). A mixture of 0.17 g (1 mmol) of *L*-serine ethyl ester hydrochloride, 0.12 g (1 mmol) of N,N'-diethylurea, 0.2 mL (2.7 mmol) of 37% aqueous formaldehyde, 0.2 mL of triethylamine (1.4 mmol), and 2 mL of ethanol was heated at reflux for 20 h, cooled, and concentrated to a residue. Chromatography using 4 : 1 ether / acetone as the eluant gave 0.22 g (80%) of **19** as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) 4.31 (s, 4 H), 4.19 (app qd, 2 H, J = 7,3), 3.87 (app t, 2 H, J = 6), 3.65 (app t, 1 H, J = 6), 3.30 (app qd, 4 H, J = 8,2), 2.37 (t, 1 H, J = 6), 1.29 (t, 3 H, J = 7), 1.11 (t, 6 H, J = 7); $[a]_D$ -50.6° (c=0.8, $CHCl_3$).

Acknowledgments: We are grateful to the Charles and Johanna Busch Memorial Fund and Merck Co. for financial support of this work, NSF grant CHEM-8300444 and NIH grant 1510RRO1486 for support of instrumentation, Rhonda Musselman for the preparation of **7** - **10**, and Profs. K. Y. Chen and Joachim Kohn for stimulating discussions.

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11. In ongoing studies we have also found that the triazone group survives hydrogenation (PtO_2, 1 atm H_2, ethanol, 48 h; Pd black, 1 atm H_2, THF, 1 h), organometallic reagents (*n*-BuLi, THF, -40°, 30 min; PhMgBr, THF, -78°, 30 min), Wittig reaction (Ph_3P=CH-CO_2Me, benzene, rt, 12 h), reduction (DIBAL, THF, rt, 3 h; $LiBH_4$, THF, 40°, 3 h), hydroxyl protection (Ac_2O, pyridine, 24 h; *t*-BuPh_2Si-Cl, DMF, imidazole, 1 h; MEM-Cl, *i*-Pr_2NEt, CH_2Cl_2, 16 h), peptide coupling (DCC, HOBT, CH_2Cl_2, 16 h), and anhydrous acids ($TiCl_4$, CH_2Cl_2, -78°, 30 min; TsOH, toluene, 12 h; neat TFA, 15 min). Triazone **24** was cleaved to phenylalanol and diethylurea by prolonged exposure to neat TFA (48 h), followed by extraction from aqueous NaOH.
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17. For example, we were unable to prepare BOC- or Z-protected 4-aminobutyraldehyde by oxidation because of their propensity to cyclize.

(Received in USA 4 January 1990)