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The Evaluation of Secondary Amine Protecting Groups for Nitration

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Abstract: Nitramines (for example RDX, HMX and CL-20) are frequently made by nitrolyzing tertiary amides. While generally high yielding, sometimes the amides can be difficult to remove while keeping any ring systems intact. This study investigates twelve acyl hexahydro-*s*-triazines for their ease of conversion into nitramines using four common nitration conditions. Several new amide protecting group have been examined and one (cyclopropanecarboxamide) has been found to be better than those amides currently employed. The amide groups have been found to be nitrolyzable in the following order: Cyclopropyl > Ethyl > Propyl > Methyl > *i*-Propyl ≈ *t*-Butyl ≈ Methoxymethyl ≫ Hydrogen > Pentafluorophenyl.

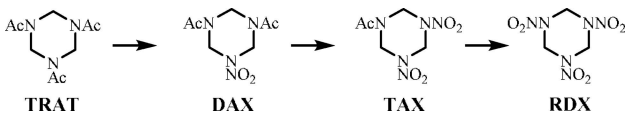
Keywords: Nitramine · Amide Nitrolysis

1 Introduction

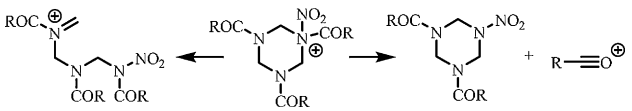
Nitramines are an important class of compounds in energetic materials. Their synthesis typically involves the reaction of precursor compounds to give cyclic or polycyclic amines which are then nitrated to give the final nitramine [1]. Examples of precursor compounds are amides (typically acetamide), sulfamides and alkyl amines (*tert*-butyl or benzyl). A good protecting group is cheap, readily available and allows for the construction and stabilization of the polycyclic ring system. It also needs to be nitrolyzable, preferably using mild reagents. These properties are not always mutually compatible.

There have been two previous studies evaluating leaving group ability for nitrations, Gilbert, et. al. [2] in 1975 and Piacenza, et. al. [3] in 1997. Both of these studies used hexahydro-*s*-triazines as their model, the nitration of which leads to RDX (1,3,5-trinitrohexahydro-*s*-triazine) (Scheme 1). We have recreated these studies using modern methods and extended them with some new examples of protecting groups. We will also give a simple calculation scheme which we use to suggest possibilities for new protecting groups. Throughout this work we will use the following nomenclature (see Scheme 1); TRAT refers to the triacylhexahydro-*s*-triazine, DAX refers to the mononitrodiacylhexahydro-*s*-triazine and TAX refers to the dinitromonoacylhexahydro-*s*-triazine without regard to the actual acyl group.

Chen, et. al. [4] has performed a very detailed analysis of the nitration of 1,3,5-triacetylhexahydro-*s*-triazine (TRAT) to RDX with nitronium ion using *ab inito* calculations. They have found that the nitronium ion initially associates with the carbonyl oxygen which is followed by its transfer to nitrogen after which the acylium ion leaves (Scheme 2). The rate limiting step is the loss of the acylium ion.



Scheme 1. Sequential nitration of 1,3,5-triacetylhexahydro-*s*-triazine.



Scheme 2. Mechanism of nitrolysis and ring opening.

Symmetrical hexahydrotriazines are a good model for examining leaving group ability for several reasons. Many different substrates are readily available and there is also the possibility of ring opening to give a methylene iminium ion (Scheme 2). This brings into play the stabilization or destabilization of the ring system.

We decided on four nitrating systems designed to highlight the relative differences in the protecting groups, these are: 1) nitronium tetrafluoroborate, 2) nitric acid / trifluoroacetic anhydride (TFAA), 3) ammonium nitrate / TFAA and 4) nitric acid / acetic anhydride. Our objective is not to synthesize RDX but to rank each protecting group according to its performance in nitrations.

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Nitronium tetrafluoroborate (NO_2BF_4) is expensive but gives a fairly pure nitronium ion. Both nitric acid / TFAA and ammonium nitrate / TFAA give trifluoroacetyl nitrate (TFAN) as the nitrating agent. Finally, nitric acid / acetic anhydride gives acetyl nitrate, the weakest nitrating medium in this study. In all cases except for NO_2BF_4 we used 2 equivalents of nitrating agent per acyl group and acetonitrile as the solvent.

Zelenov [5] has recently shown that in the presence of excess nitric acid, TFAN gives N_2O_5 and trifluoroacetic acid (TFA). Gilbert's (50 eq. HNO_3 : 10 eq. TFAA) and Piacenza's (120 eq. HNO_3 : 24 eq. TFAA) conditions are therefore equivalent to nitrogen pentoxide in nitric acid. These conditions are much stronger than TFAN on its own.

2 Experimental Section

2.1 General Considerations

The compounds and reactions reported below show various levels of air- and moisture sensitivity, therefore all manipulations were carried out under nitrogen unless otherwise noted. Trioxane (Sigma), anhydrous acetonitrile (99.8 %, Aldrich), propionitrile (Aldrich), isobutyronitrile (Aldrich), pivalonitrile (Aldrich), cyclopropanecarbonitrile (AK Scientific), butyronitrile (Sigma), benzonitrile (Sigma), 4-nitrobenzonitrile (Aldrich), 3,5-dichlorobenzonitrile (AK Scientific), pentafluorobenzonitrile (Sigma), methoxyacetonitrile (AK Scientific), concentrated sulfuric acid (Sigma), acetic anhydride (Sigma), fuming nitric acid (99 %, Sigma), trifluoroacetic anhydride (Sigma), and acetic anhydride (Sigma) were all used as received. Nitronium tetrafluoroborate (Sigma) was washed with dry, ethyl acetate, and stored in a N_2 filled glovebox. Ammonium nitrate (Sigma) was ball milled into a fine powder and dried under vacuum. 1,3,5-triformylhexahydro-*s*-triazine [2], 1,3,5-triacetylhexahydro-*s*-triazine [6], 1,3,5-tripropionylhexahydro-*s*-triazine [6], 1,3,5-triisobutyroylhexahydro-*s*-triazine [2], 1,3,5-pivaloylhexahydro-*s*-triazine [2], 1,3,5-tribenzoylhexahydro-*s*-triazine [7], and 1,3,5-tri(methoxyacetyl)hexahydro-*s*-triazine [2] were all synthesized using methods previously described in the literature, whereby each was fully characterized and found to match the results observed in the literature.

2.2 Spectroscopic Methods

NMR spectra were collected on a Bruker Avance 500 MHz spectrometer in solutions of $CDCl_3$, acetonitrile-d_3 or DMSO-d_6. Chemical shifts are reported using the standard δ notation in parts per million. Infrared spectroscopy was performed on a Thermo Nexus spectrometer at 4 μ resolution using an MCTA liquid nitrogen cooled detector (8 scans). Gas chromatography-mass spectroscopy (GC-MS) data were collected on DCM solutions of analyte on a Thermo trace 1310 gas chromatograph with an exactive orbitrap detector using a temperature method of three minutes at 40 °C, a temperature ramp of 20 °C per minute until reaching 300 °C, and finally ten minutes at 300 °C. Direct Insertion probe (DIP) analysis was performed on a Thermo scientific DSQII equipped with a direct probe controller using a method starting at 40 °C and a temperature ramp of 5 °C per minute until reaching a maximum temperature of 450 °C. Differential scanning calorimetry (DSC) studies were performed on a TA Instruments Q200 differential scanning calorimeter to test purity and determine the melting points for the series of triazine ring systems. Samples were contained in hermetically sealed, aluminum pans under a stream of N_2 gas with a flow rate of 50 mL per minute. High purity indium was used to calibrate the calorimeter. DSC scans were performed on 2.5–5.0 mg samples. Elemental analysis were performed by Atlantic Microlab, Inc. and testing was done for carbon, hydrogen, nitrogen and chlorine.

2.3 Sample Analysis

A typical quantitative NMR (qNMR) experiment consisted of a 0.75 mL acetonitrile-d_3 (or DMSO-d_6 when noted) solution of 10–20 mg of sample. 10 μL of benzene (or toluene when DMSO was used) was added as an internal standard. In the case of 1,3,5-triformylhexahydro-*s*-triazine, the contents were heated to 85 °C to coalesce any rotational isomers. The amount of analyte (TRAT to RDX) in the sample was determined based on the relative integral to the benzene standard. This was then converted into molar yields using eq 1.

$$\%Yield = 100 \times \frac{(moles\ in\ NMR)}{(moles\ Triazine)} \times \left(\frac{wt\ crude}{wt\ NMR\ samp}\right) \qquad (1)$$

2.4 Triazine Synthesis

1,3,5-tricyclopropionylhexahydro-*s*–triazine. A 500 mL 3-neck round bottom flask was charged with trioxane (5.03 g, 55.9 mmol), cyclopropanecarbonitrile (25 mL, 329 mmol, 6 eq.), 1,2-dichloroethane (25 mL), and a magnetic stir bar. The flask was equipped with a reflux condenser open to air. The flask was cooled to 5 °C in an ice bath. Concentrated sulfuric acid (0.5 mL, 9.33 mmol) was added. The reaction mixture was stirred in the ice bath for 20 minutes and then allowed to slowly warm to room temperature. At roughly 22 °C, a large exotherm was observed, use extreme caution. After the exotherm was complete, the reaction mixture was slowly heated in an oil bath to 80 °C and kept there for 90 minutes. The mixture remained homogenous. The flask was cooled to room temperature, whereby a white precipitate crashed out of solution. The solid was collected on

a glass fritted filter and washed with copious amounts of hexanes (500 mL) then dried at room temperature inside a vacuum oven for 18 hours to yield the product as a white powder (9.39 g, 58%) with a $M.P._{DSC}$ of 168.2 °C. Anal. Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.37; H, 7.30; N, 14.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45 (s, 6H, N–CH_2–N), 1.95 (br s, 3H, C(C=O)–CH), 0.944 (s, 6H, cyclopropyl –CH_2), 0.830 (m, 6H, cyclopropyl –CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.6 (s, C=O), 56.54 (s, N–CH_2–N), 11.08 (s, cyclopropyl sp^3 CH), 8.32 (s, cyclopropyl –CH_2). IR (cm^{-1}) (solid): 3067–3010, 1638 (C=O), 1434 (cyclopropane ring), 1080–1360 (C–N stretch). GC-MS (DCM): 16.87 min. (263 *m/z* = [M^+-cyclopropane], 222 *m/z* = [M^+ - C(=O)-cyclopropane], 181 *m/z* = [M^+ - (C(=O)-cyclopropane)-cyclopropane], 154 *m/z* [M^+-(C(=O)-cyclopropane)$_2$].

1,3,5-tri(3,5-dichlorobenzoyl)hexahydro-*s*-triazine. A 500 mL 3-neck round bottom flask was charged with 3,5-dichlorobenzonitrile (7.76 g, 45.1 mmol, 3.9 eq.) and a magnetic stirring bar. The flask was equipped with a reflux condenser, an addition funnel and sealed with a rubber septum. The solid was dissolved in 1,2-dichloroethane (50 mL) and lowered into an oil bath. Concentrated sulfuric acid (0.15 mL, 2.8 mmol) was added to the solution. The reaction mixture was heated to 80 °C. Once at 80 °C, a solution of trioxane (1.035 g, 11.5 mmol) and acetic anhydride (0.30 mL, 3.2 mmol) in 1,2-dichloroethane (50 mL) was added dropwise over the course of 30–60 minutes. A slight precipitate was observed to crash out upon addition. The reaction mixture was then kept at 80 °C overnight. The flask was removed from heat and cooled to room temperature, filtered through Celite on a glass fritted filter. The filtrate volatiles were removed on a rotary evaporator. The concentrated solution was diluted with DI water (500 mL) to induce precipitation of a white material. The solid was collected on a glass fritted filter and washed with toluene (20 mL) and hexanes (3×20 mL). The solid was dried under vacuum overnight to yield the product as a white powder (3.47 g, 50%) with a $M.P._{DSC}$ of 215.2 °C. Anal. Calcd for $C_{24}H_{15}Cl_6N_3O_3$: C, 47.56; H, 2.49; Cl, 35.09; N, 6.93. Found: C, 47.26; H, 2.65; Cl, 34.92; N, 6.90. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 3H, *p*-CH), 7.37 (s, 6H, *o*-CH), 5.34 (s, 6H, N–CH_2–N). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.3 (s, C=O), 135.8 (s, C–Cl), 131.6 (s, *p*-CH), 126.4 (s, *m*-CH), 58.5 (s, N–CH_2–N). IR (cm^{-1}) (solid): 3076 (aryl-CH), 1662 (C=O), 1565 (aryl C–C), 1416 (aryl C=C), 1268.9 (C–N), 1101 (C–Cl). GC-MS (DIP probe): 6.24–8.45 min. (605 *m/z* = [M^+]).

1,3,5-tri(4-nitrobenzoyl)hexahydro-*s*-triazine. Using a similar procedure as for 1,3,5-tri(3,5-dichlorobenzoyl)hexahydro-*s*-triazine. Trioxane (1.04 g, 11.6 mmol), 4-nitrobenzonitrile (5.75 g, 38.8 mmol, 3.3 eq.), 1,2-dichloroethane (100 mL), acetic anhydride (0.30 mL, 3.2 mmol), H_2SO_4 (0.15 mL, 2.8 mmol). After cooling to room temperature, the precipitated solid was collected on a sintered glass filter. The solid was washed with acetone (200 mL), 1,2-dichloroethane (200 mL), and hexanes (200 mL). The off-white solid was dried under high vacuum overnight to yield the product (5.14 g, 83%) with a $M.P._{DSC}$ observed at 292.3 °C. Anal. Calcd for $C_{24}H_{18}N_6O_6$: C, 53.94; H, 3.39; N, 15.73. Found: C, 53.47; H, 3.43; N, 15.57. ^{1}H NMR (500 MHz, DMF-d_7): δ 8.26 (br s, 6H, aryl-H), 7.79 (br s, 6H, aryl-H), 5.51 (br s, 6H, N–CH_2–N). IR (cm^{-1}) (solid): 1651, 1604, 1533, 1418, 1347, 1275. GC-MS (DIP probe): 7.91–10.77 min. (534 *m/z* = [M^+]).

1,3,5-tri(pentafluorobenzoyl)hexahydro-*s*-triazine. Using a similar procedure as for 1,3,5-tri(3,5-dichlorobenzoyl) hexahydro-*s*-triazine. Trioxane (1.00 g, 11.1 mmol), pentafluorobenzonitrile (5.5 mL, 45 mmol, 4.0 eq.), 1,2-dichloroethane (100 mL total), acetic anhydride (0.30 mL, 3.2 mmol), H_2SO_4 (0.15 mL, 2.8 mmol). After heating at 85 °C for four hours, the reaction mixture was cooled to room temperature. The volatiles were removed using a rotary evaporator to remove the majority of 1,2-dichloroethane. The contents were extracted with dichloromethane, washed with a saturated $NaHCO_3$ solution, brine, DI H_2O, 1 M KOH solution, and again with DI water. The organic phase was dried with magnesium sulfate, filtered, and the volatiles were removed on a rotary evaporator. The sticky solid was rinsed with hexanes and the solid was collected on a glass fritted filter. The solid was suspended in acetonitrile and filtered via Buchner funnel. The collected filtrate volatiles were removed to yield a pale yellow oil, which upon cooling to room temperature began to solidify. The solid was rinsed with hexanes and dried under high vacuum to yield a pale yellow solid. The material was subjected to column chromatography to isolate the product as a white powder (2.61 g, 35%) with no observable melting point ($M.P._{DSC}$) out to 400 °C. Anal. Calcd for $C_{24}H_6F_{15}N_3O_3$: C, 43.07; H, 0.90; F, 42.58; N, 6.28. Found: C, 42.64; H, 0.89; F, 42.24; N, 6.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.35 (s, 6H, –CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 158.1 (s, C=O), 144.5 (br s, –CF)), 144.1 (br s, –CF), 142.5 (br s, –CF), 142.1 (br s, –CF), 138.9 (br s, –CF), 136.9 (br s, –CF), 108.5 (br s, C), 57.1 (s, (N–CH_2–N). ^{19}F NMR (470 MHz, $CDCl_3$): δ −139.7, −148.7, −158.8. IR (cm^{-1}) (solid): 1676, 1504, 1431, 1322, 1246, 1103, 995. GC-MS (DCM): 16.82 min. (669 *m/z* = [M^+]).

2.5 General Nitration Conditions

Nitronium tetrafluoroborate. A 25 mL two neck flask was charged with a magnetic stirbar and nitronium tetrafluoroborate (3.1 eq.) inside a N_2 filled glovebox. The flask was sealed with two rubber septa, removed from the glovebox and immediately placed under a steady N_2 flow. The flask was outfitted with a 14/20 thermometer adaptor and a N_2 bubbler. The flask was cooled to 5 °C in an ice bath. Anhydrous acetonitrile (10 mL) was then added using a disposable syringe and the contents were allowed to stir for 30 minutes. Solid triazine (~0.5 mmol) was then added to the flask using an additional 1 mL of anhydrous acetonitrile to help transfer any remaining solid. The flask was stirred at 5 °C for an additional 20 minutes. The flask was then re-

moved from the ice bath and allowed to slowly warm to room temperature over the course of two hours. After two hours, the mixture was quenched with DI H_2O (10 mL) and extracted with ethyl acetate (120 mL). The organic layer was washed with copious amounts of DI H_2O and brine (500 mL), dried with magnesium sulfate, filtered through a Buchner funnel, and the volatiles were removed on a rotary evaporator. The residue was dissolved in 5 mL of acetonitrile and transferred to a 20 mL scintillation vial and the volatiles were removed again by rotary evaporation. The residue was then washed with 5 mL aliquots of hexanes and decanted (3 times) and the resulting residue was dried under high vacuum overnight.

Nitric Acid/trifluoroacetic anhydride. A 25 mL two-neck flask was charged with anhydrous acetonitrile (10 mL) and a magnetic stirbar. The flask was sealed with a 14/20 thermometer adaptor and an N_2 bubbler. The flask was cooled in an ice bath to 5 °C for 30 minutes at which point trifluoroacetic anhydride (6 eq.) was added using a disposable syringe. The contents were stirred for an additional 15 minutes at which point fuming nitric acid (99%, 6 eq.) was added using a syringe. The reaction mixture was stirred in the ice bath for 30 minutes. Solid triazine (~0.5 mol) was then added using 1 mL of anhydrous acetonitrile to help transfer any residual solid. After an additional 20 minutes of stirring at 5 °C, the reaction flask was removed from the ice bath and allowed to slowly warm up to room temperature over the course of two hours. After two hours, the mixture was quenched with DI H_2O (10 mL) and extracted with ethyl acetate (120 mL). The organic layer was washed with copious amounts of DI H_2O and brine (500 mL), dried with magnesium sulfate, filtered through a Buchner funnel, and the volatiles were removed on a rotary evaporator. The residue was dissolved in 5 mL of acetonitrile and transferred to a 20 mL scintillation vial and the volatiles were removed again by rotary evaporation. The residue was then washed with 5 mL aliquots of hexanes and decanted (3 times) and the resulting solid material was dried under high vacuum overnight.

Ammonium nitrate/trifluoroacetic anhydride. A 25 mL two neck flask was charged with ammonium nitrate (6 eq.) and a magnetic stirbar. The flask was sealed with a 14/20 thermometer adaptor and a N_2 bubbler. The flask was cooled to 5 °C in an ice bath, at which point anhydrous acetonitrile (10 mL) was added using a disposable syringe to create a milky suspension. The mixture was stirred for 15–20 minutes. To the mixture was then added trifluoroacetic anhydride (10 eq.), resulting in the suspension becoming more of a solution. The flask was stirred at 5 °C for an additional 30 minutes. Solid triazine (~0.5 mmol) was then added using an additional 1 mL of anhydrous acetonitrile to help transfer remaining residue. The contents were stirred in an ice bath for an additional 20 minutes, at which time the flask was removed from the ice bath and allowed to warm to room temperature overnight. After 18 hours, the mixture was quenched with DI H_2O (10 mL) and extracted with ethyl acetate (120 mL). The organic layer was washed with copious amounts of DI H_2O and brine (500 mL), dried with magnesium sulfate, filtered through a Buchner funnel, and volatiles removed on a rotary evaporator. The residue was dissolved in 5 mL of acetonitrile and transferred to a 20 mL scintillation vial and the volatiles were removed again by rotary evaporation. The residue was then washed with 5 mL aliquots of hexanes and decanted (3 times) whereby the resulting solid material was dried under high vacuum overnight.

Nitric Acid/acetic anhydride. A 25 mL two-neck flask was charged with anhydrous acetonitrile (10 mL) and a magnetic stirbar. The flask was sealed with a 14/20 thermometer adaptor and an N_2 bubbler. The flask was cooled in an ice bath to 5 °C for 20 minutes at which point acetic anhydride (6 eq.) was added. Contents were stirred for an additional 15 minutes at which point fuming nitric acid (99%, 6 eq.) was added using a syringe. The reaction mixture was stirred in the ice bath for 30 minutes then allowed to warm to room temperature for 30 minutes. The flask was re-cooled to 5 °C, at which point solid triazine (~0.5 mol) was then added using 1 mL of anhydrous acetonitrile to help transfer any residual solid. After an additional 20 minutes of stirring at 5 °C, the reaction flask was removed from the ice bath and allowed to slowly warmed to room temperature over the course of two hours. After two hours, the mixture was quenched with DI H_2O (10 mL) and extracted with ethyl acetate (120 mL). The organic layer was washed with copious amounts of DI H_2O and brine (500 mL), dried with magnesium sulfate, filtered through a Buchner funnel, and the volatiles were removed on a rotary evaporator. The residue was dissolved in 5 mL of acetonitrile and transferred to a 20 mL scintillation vial and the volatiles were removed again by rotary evaporation. The residue was then washed with 5 mL aliquots of hexanes and decanted (3 times) whereby the resulting solid material was dried under high vacuum overnight.

3 Results and Discussion

As can be seen from the results in Table 1, cyclopropanecarboxamides are better than even the propionamides in their nitrolyzability. The higher *s* character in the exocyclic bonds enables greater conjugation with the ring enhancing its electron donor ability. In addition, the carbons are pinned back making their steric demands less pronounced.

The high yields (up to 71% RDX) when employing NO_2BF_4 as the nitrating agent at only 3.1 equivalents demonstrates just how efficient this reagent is.

Both Gilbert and Piacenza found that amides are the preferred protecting groups and that electron donating groups on the amides enhance nitration. Conversely, electron withdrawing groups (for example carbamates or methoxyacetyl) hinder nitration. In addition, there can be a

Table 1. Experimental yields for nitrations of 1,3,5-triacyl-1,3,5-hexahydro-*s*-triazines.

	This work	This work	This work	This work	Gilbert	Piacenza
Reagents	NO_2BF_4	HNO_3:TFAA	NH_4NO_3:TFAA	HNO_3:Ac_2O	HNO_3:TFAA	HNO_3:TFAA
Equivalents	3.1	6:6	6:10	6:6	50:10	120:24
Temp	5 °C–25 °C	5 °C–25 °C	5 °C–25 °C	5 °C–25 °C	50 °C	60 °C
Time	2 hrs	2 hrs	18 hrs	2 hrs	30 min	30 min
R=						
H	7% di	12% di	5% di	2% mono	0% RDX	
	2% mono	2% mono	4% mono			
Me	28% RDX	31% RDX	2% RDX	8% mono	80% RDX	69% RDX
	52% di	55% di	40% di	4% sm	4% di	5% di
Et	68% RDX	72% RDX	14% RDX	5% di	98% RDX	91% RDX
	28% di	11% di	37% di	30% mono		
Propyl	35% RDX	55% RDX	9% RDX	1% di	94% RDX	
	33% di	20% di	75% di	84% mono		
i-Pr	8% RDX	4% RDX	1% RDX	54% mono	94% RDX	93% RDX
	75% di	52% di	58% di	25% sm		
Cyclopropyl	71% RDX	89% RDX	42% RDX	13% di		
	16% di		24% di	67% mono		
t-Butyl	14% RDX	6% RDX	44% di	–	15% RDX	22% RDX
	7% di	64% di				
	18% mono					
Methoxymethyl	3% RDX	4% RDX	22% di	2% mono		
	40% di	48% di				
Phenyl	a	a	a	a		a
3,5-Dichlorphenyl	b	b	b			
4-Nitrophenyl	insol	insol	insol	insol		
Pentafluorophenyl	17% mono	48% sm	3% mono	53% sm		
	57% sm		45% sm			

Yields are mole% (see experimental section), di refers to dinitration or TAX, mono refers to mononitration or DAX and sm refers to starting material or TRAT. a) See text. b) Mixture of mono, di and tri-nitration on the aromatic ring.

strong steric component (pivalamides show little or no nitration).

In our hands, TFAN gave similar or better results than nitronium tetrafluoroborate. This is likely related to the stoichiometry employed. Acetyl nitrate was only able to place one or two nitro groups on the ring, typically with considerable decomposition.

Steric effects are more pronounced in the current work than in either Gilbert's or Piacenza's work. They found a sharp decrease in yields on going from the *i*-propyl group to the *t*-butyl group. We find the drop on going from the ethyl to the propyl group and the effect is more subtle. The temperature of nitration as well as stoichiometry are probably determining factors.

3.1 Calculating ΔE

The nitrolyzability of protecting groups is related to the stability of the corresponding acylium ion. By calculating the change in energy for the reaction $RCOX + NO_2^+ \rightarrow RCO^+ + XNO_2$, where X is any group, we can evaluate the relative stability of various acylium ions. By relating their stability to acetyl (R=Me), the energies of both NO_2^+ and XNO_2 cancel. We therefore need calculate only the energies for RCOX and RCO^+. In Table 2, X is NH_2 but we found similar results with Cl.

We are not interested in the absolute values for this change in energy only in their relative placements. One word of caution, there is no inclusion of sterics in this calculation and if a nitrolysis proceeds via a different mechanism (such as with *t*-butoxycarbamates) then the results are invalid. This can be seen in the series methyl, ethyl, *i*-propyl, *t*-butyl in which the *t*-butyl is the most negative, yet we see little nitration when it is the leaving group.

Table 2 shows the results of the calculations using acetyl as a baseline. The calculations were performed using Gaussian16 W [8] with the B3LYP functional and the 6-311++(2df,2p) basis set. All compounds have been fully optimized and have no negative frequencies. In Table 2, a negative number (also in **bold**) indicates that the acylium ion is stabilized and should reflect a group more easily nitrolyzed than acetyl.

These results are in line with what Gilbert and Piacenza found and what we see in this report. Formyl $\ll$ acetyl $<$ propionyl $\approx$ *i*-butyryl. The cyclopropyl entry is new and represents one of the best possibilities for a protecting group. It gives higher yields than even the propionamide group, although the difference is small. It seems to have a good balance of electron donating ability and steric bulk. It also has

Table 2. ΔE for $RCOX + NO_2^+ \rightarrow RCO^+ + XNO_2$ (Relative to Acetyl, R=Me)

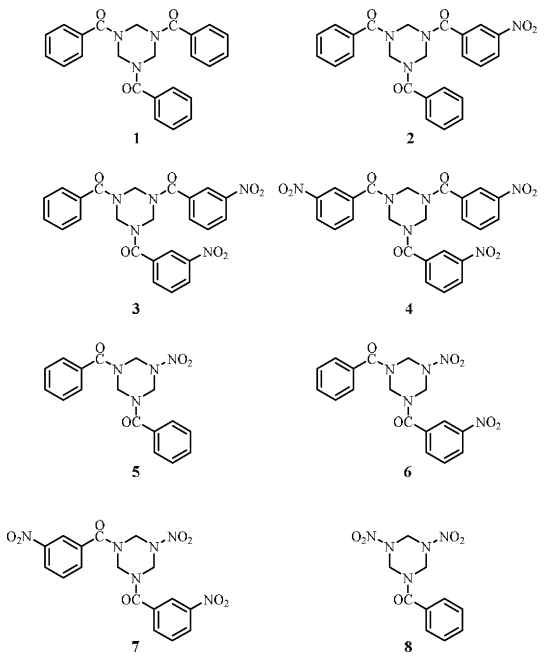
R =	X=NH_2 kcal/mole
H	+34.3
Methyl	0.0
Ethyl	**−5.7**
Propyl	**−8.9**
i-Propyl	**−10.6**
Cyclopropyl	**−11.2**
t-Butyl	**−16.0**
Methoxy	+13.7
Dimethylamino	**−15.0**
Methoxymethyl	+2.7
Trimethylsilyl	**−31.2**
Trimethylsilylmethyl	**−23.8**
Phenyl	**−17.3**
3-Nitrophenyl	**−7.8**
4-Nitrophenyl	**−7.6**
3,5-Dichlorophenyl	**−7.5**
4-Cyanophenyl	**−5.5**
Pentafluorophenyl	+1.1

the advantage that the deprotonation of the acylium ion to give a ketene is discouraged.

3.2 Aromatic Groups

The aromatic systems were somewhat surprising. Even nitrated benzamides calculate to be better leaving groups than acetyl (Table 2). However, without the inclusion of steric effects we needed to examine them experimentally.

This lead us to attempt to find aromatic systems less susceptible to nitration on the aromatic ring such as 3,5-dichlorophenyl and 4-Nitrophenyl. *tris*-(4-Nitrobenzoyl)hexahydro-*s*-triazine turned out to be too insoluble to be used. *tris*-(3,5-Dichlorobenzoyl)hexahydro-*s*-triazine gave only nitration on the aromatic ring in a mixture which was too complicated to analyze. We then turned to determining exactly what compounds were formed in the nitration of 1,3,5-tribenzoylhexahydro-*s*-triazine (Scheme 3)



Scheme 3. Compounds formed from nitration of *tris*-benzoylhexahydro-*s*-triazine.

All of the compounds in Scheme 3 except for compound **6** were found during the nitration of *tris*-benzoylhexahydro-*s*-triazine. Table 3 shows their yields for the four types of nitrations in this study. Piacenza found that the phenyl rings nitrated after which the product precipitated from the nitrating mixture. We did not see precipitation of nitrated products due to our use of acetonitrile as the solvent.

The phenyl ring is much more suseptible to nitration than the amide is. Each ring is sequentially nitrated until the trinitro derivative (**4**) is produced. Compound **4** is nitrolyzable to give compound **7** but this reaction is slow.

We did not see RDX in these nitrations. We wanted to see if we could push the reaction in the direction of RDX by increasing the stoichiometry of the nitration. Using nine equivalents of TFAN resulted in only a small increase in the yield of compound **7** suggesting that nitrolysis is very slow.

Table 3. Compounds formed from the nitrolysis of *tris*-benzoylhexahydro-*s*-triazine.

Cmpd Eq.	NO_2BF_4 3.1	HNO_3:TFAA 6:6	NH_4NO_3:TFAA 6:6	HNO_3:Ac_2O 6:6	HNO_3:TFAA 9:9
1	0%	0%	1%	76%	0%
2	5%	0%	0%	19%	0%
3	49%	1%	17%	0%	2%
4	16%	42%	62%	0%	43%
5	0%	0%	0%	5%	0%
6	0%	0%	0%	0%	0%
7	3%	31%	19%	0%	36%
8	1%	0%	0%	0%	0%

4 Conclusion

We have found that the ease of nitrolysis for amide protecting groups is cyclopropylcarboxamide > propionamide > butryamide > acetamide > *i*-butryamide ≈ pivalamide ≈ methoxyacetamide ⩾ formamide > pentafluorobenzamide. We are in the process of using cyclopropylcarboxamide protecting groups in our studies attempting to make polycyclic nitramines.

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