Improved synthesis of an energetic material, 1,3,3-trinitroazetidine (TNAZ) exploiting 2-iodoxy benzoic acid (IBX) as an oxidising agent

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Tetrahydropyranyl protected 1,3-dihalo-2-propanol reacts with *p*-toluene sulfonamide in the presence of K_2CO_3 to give corresponding N-*p*-tosyl-3-azetidinol. Deprotection and oxidation with iodoxy benzoic acid followed by oximation of N-*p*-tosyl-3-azetidinone readily affords the corresponding azetidine oxime in almost quantitative yield. The subsequent oxidative nitrolysis of oxime gives 1,3,3-trinitroazetidine (TNAZ) through a new sequence of reactions with excellent purity (> 99%) and moderate yield (40%).

Keywords: Trinitroazetidine, strained ring, 2-iodoxy benzoic acid, oximination, synthesis, oxidative nitrolysis , insensiive munitions

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Strained polynitro-cyclic compounds are the fore-front of research for more powerful and less sensitive energetic materials. An important new member of this class of energetic materials is 1,3,3-trinitroazetidine (TNAZ), a new powerful and steam castable strained ring explosive which is of considerable interest to US Military agency. Among its favourable properties are a low melting point (101 °C), moderate density (1.84 g/cm^{3}), good thermal stability (>240 °C) and low sensitivity[1]. In an effort to improve the synthetic strategies and an increasing number to the applications for insensitive munitions in the recent years elucidate the worldwide interest in this new heterocyclic system. However, the principal source of 1,3,3-trinitroazetidine[2-4] remains the original preparative method starting from *tert*-butyl amine and epichlorohydrin, despite the overall poor yield. The present report describes the results of the full investigation and experimental details of a new alternate synthesis where the key roles are played by protection of a secondary hydroxyl group with low cost reagent to affect azetidine ring closure and oxidative nitrolysis for the simultaneous introduction of the N-NO_2 and C $(NO_2)_2$ groups.

Results and Discussion

Strategy adopted in our approach to develop the synthesis route of TNAZ is based on earlier report[5] where similar transformations in the related systems were observed. An attractive feature of this route is that HNO_3 oxidation leading to the formation of $C(NO_2)_2$ group is combined in one step, with the nitroylsis of the N-substituent to produce the NNO_2 function (**Scheme I**). An added benefit of this approach is that all energetic nitro groups would be introduced only in the final step of the synthesis which is desirable from a safety viewpoint.

Obviously, 3-azetidinones are the key intermediate to this method. 1-Alkyl-3-azetidine can be conveniently synthesized by using the method of Gartner[6] and also by others[7]. However, the oxidative procedures for converting 1-*tert*-butyl-3-azetidine led to unstable ketones[8]. We also failed to achieve the stable product of azetidinone when the reactions were carried out with other oxidizing agent such as iodoxy benzoic acid. The further reaction of N-acetyl-3-hydroxyazetidine with iodoxybenzoic acid did not lead to the formation of desired product azetidinone. Finally, cyclisation to azetidine rings with N-tosyl group was accomplished by the reaction of 1,3-dihalo-2-propanol with *p*-toluene sulphonamide in the presence of potassium carbonate. Azetidine ring closure in the reaction of amines with either of tetrahydropyranyl or trimethyl silyl ether of 1,3-dichloro-2-propanol which is reported to require
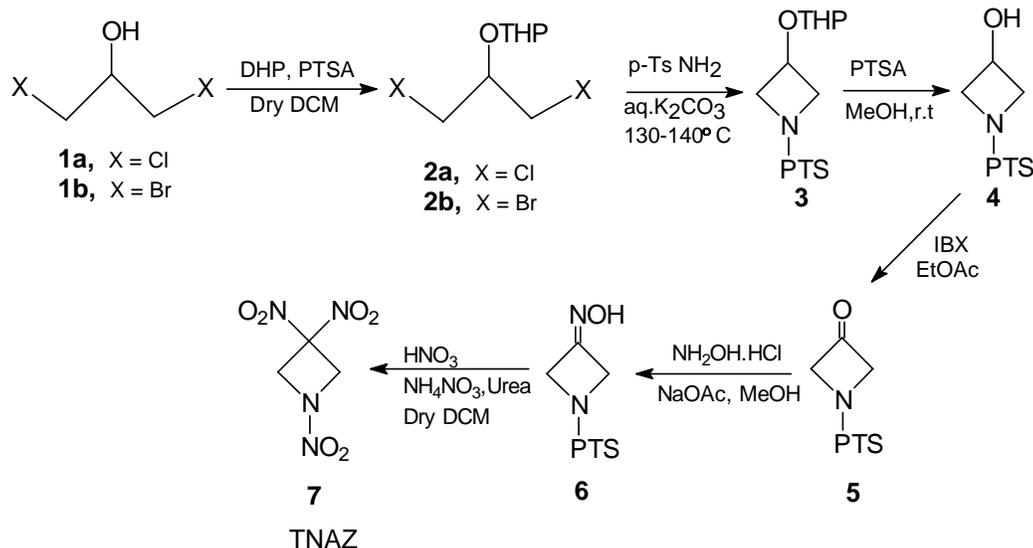
Scheme I

extensive reaction time periods[9] has been reduced to 30 hr. This further afforded improved yield when the reaction was carried out in DMF at 130-40 °C. Subsequently, deprotection with *p*-toluene sulfonic acid in methanol afforded N-*p*-tosyl-3-azetidinol in near quantitative yield.

Transformation of N-tosyl-3-azetidinol **4** to ketone **5** was affected in 94% yield by oxidation with iodoxybenzoic acid in a facile manner. As mentioned earlier, using the same reagent iodoxybenzoic acid, the corresponding ketones of *tert*-butyl or acyl derivatives could not be achieved. Later, the ketone **5** on treatment with hydroxylamine hydrochloride afforded N-*p*-tosyl-3-azetidine oxime in quantitative yield. In the final step, the oxime was treated with 99% HNO_3 in refluxing methylene chloride to simultaneously nitrolyze the *p*-tosyl group and oxidize the oxime function to produce in 40% yield the desired 1,3,3-trinitroazetidine (TNAZ).

All important intermediate compounds prepared in the course of achieving the target compound TNAZ, have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and micro-elemental analyses. The purity of TNAZ was determined by HPLC with a mobile phase methanol-water (70:30) at a flow rate of 1 ml / min in C-18 micro bondapack column with UV detector at 232 nm at a retention time of 2.32 min. The analysis of results indicated the purity of compound > 99% . IR vibrational stretching signals at 3000 cm^{-1} are due to high ring tension of the heterocyclic system with evidence of NO, NO_2 and N-N stretching vibrations. The chemically and

magnetically equivalent four protons of the ring occur as singlet at δ 5.45 ppm. In ^{13}C NMR spectrum the two secondary ring carbon atoms resonate as strong singlet at δ 63.2 ppm while a typical weak signal can be found for a quaternary carbon at 103.3 ppm. The EIMS showed no molecular ion peak but nevertheless some characteristic values for structure information were found. The major fragmentation pathways involve the loss of NO_2 or nitrous acid from the dinitromethylene group followed by a loss of nitro group or NO from the nitramine group. The chemical ionization mass spectrometry in methane was also carried out on Finigan Mass Spectrometer where M[+1] peak (100%) along with other diagnostic peaks with rich abundance were observed.

Experimental Section

General. All yields are unoptimised. Elemental analysis was performed by elemental analyzer EA-1101. Melting points were measured using a Mettler FP-61 automatic melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infra Red Spectrophotometer using KBr matrix. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker-300 MHz instrument with tetramethyl silane as an internal standard and chemical shifts are recorded in δ values. Electron impact mass spectra were measured on a double focusing JEOL-DS Mass Spectrometer at 70 eV using direct insertion technique. The chemical ionization mass spectrometry in methane was carried on Finnigan Mass Spectrometer.

All solvents were obtained from commercial sources and used without further purification unless otherwise noted. Tetrahydrofuran (THF) was distilled from Na/benzophenone prior to use, dichloromethane (DCM), *p*-toluene sulfonic acid (PTSA), *p*-toluene sulfonamide, dihydropyran (DHP) and anhydrous potassium carbonate were purchased from E.Merck. Hydroxylamine hydrochloride, sodium acetate, ammonium nitrate, anthranilic acid, sodium nitrate, potassium iodide and potassium bromate were the products from Qualigens Fine Chemicals.

1,3-Dichloro-2-(tetrahydropyranyl) propane 2a. To a solution of 1,3-dichloro-2-propanol (64.5 g, 0.1 mole) and *p*-toluene sulfonic acid (1.88 g, 0.01 mole) in dry dichloromethane (500 mL) under argon atmosphere at 0 °C was added dihydropyran (DHP) (62.5g, 0.75 mole) drop by drop through addition funnel for the period of half an hour. After the addition was complete, the reaction mixture was stirred further for 10 minutes at 0 °C and then allowed to come to room temperature and stirred for another 2 hr at this temperature. Reaction mixture was poured in 200 mL of water and the organic layer washed with 2×100 mL of saturated NaHCO₃ and 200 mL of brine solution. The organic layer was dried over Na₂SO₄ and solvent was evaporated under reduced pressure. Residue was distilled under reduced pressure to get the desired product **2a** in 95% yield (99.8 g), b.p 68 °C / 1 Hg mm. Anal. Calcd for $C_8H_{14}Cl_2O_2$: C, 45.09; H, 6.58. Found: C, 44.78; H, 6.32% ; IR (KBr): 3024, 2946, 1624, 1426, 1342, 1028 cm^{-1} ; ^{1}HNMR (CDCl₃): δ 1.5 (m, 6H), 3.75 (m, 8H).

1,3-Dibromo-2-[(tetrahydro-2*H*-pyran-2-yl) oxy] propane 2b. This compound was prepared by the procedure described for the dichloro isomer **2a**, yield, 96% , b.p. 75 °C / 1 Hg mm. Anal. Calcd for $C_8H_{14}Br_2O_2$: C, 31.81; H, 4.64. Found: C, 31.62; H, 4.44% ; IR (KBr): 3024, 2944, 1624, 1426, 1342, 1028, 684 cm^{-1}; ^{1}HNMR (CDCl₃): δ 1.4 (m, 6H), 3.75 (m, 8H).

1-(*p*-Tosyl)-3-[(tetrahydro-2*H*-pyran-2-yl) oxy] azetidine 3. To a solution of *p*-toluene sulfonamide (51.36 g, 0.3 mole) and anhydrous potassium carbonate (55 g, 0.4 mole) in dry dimethylformamide under an argon atmosphere was added 1,3-dichloro-2-(tetrahydropyranyl) propane (42.6 g, 0.2 mole) drop by drop with syringe for half an hour. The mixture was refluxed on an oil-bath at 130-40 °C for 30 hr. Solvent was removed under reduced pressure below 60 °C to avoid polymerization. The compound was purified by column chromatography using 10% ethyl

acetate in petroleum ether. A colourless low melting liquid was obtained in 60% yield (37.32 g), m.p. 60 °C. Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.85; H, 6.8; N; 4.5. Found: C, 57.03; H, 6.78; N, 4.43% ; IR (KBr): 2948, 2846, 1598, 1466, 1160, 1036, 868, 801, 668, 606, 550 cm^{-1},^{1}HNMR (CDCl₃): δ 1.5 (m, 6H), 2.45 (s, 3H), 3.65 (m, 4H), 4.0 (t, 2H), 4.35 (m, 1H), 4.5 (t, 1H), 7.6 (d, 2H), 7.75 (d, 2H).

1-*p*-Toluenesulfonylazetidine-3-ol 4. A mixture of 1-(*p*-toluenesulfonyl)-3-(tetrahydropyranyl) azetidine (62.2 g, 0.2 mole) and *p*-toluenesulphonic acid (0.76g, 0.004 mole) in methanol (500 mL) was stirred at ambient temperature for 20 hr. The mixture was concentrated under vacuum and the resulting residue was partitioned between water and methylene chloride. The organic phase was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulphate and filtered. The filtrate was concentrated under vacuum to give **4** in quantitative yield, m.p. 103 °C. Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.76; N, 6.16. Found: C, 53.05; H, 5.91; N, 6.06% ; IR (KBr): 3294, 3044, 2934, 1466, 1340, 1166, 1112, 1022, 680, 542 cm^{-1}; ^{1}HNMR (CDCl₃): δ 2.5 (s, 3H), 2.6 (br, s, 1H), 3.6 (t, 2H), 4.05 (t, 2H), 4.5 (m, 1H), 7.4 (d, 2H), 7.8 (d, 2H).

1-(*p*-Toluenesulfonyl) azetidine-3-one 5. To a solution of **4** (45.4 g, 0.2 mole) in ethyl acetate (400 mL) was added 2-iodoxybenzoic acid[10] (112g, 0.4 mole). The reaction mixture was refluxed for 20 hr, filtered, and the filtrate was concentrated under reduced pressure to yield **5** in 94% yield (42.3 g), m.p. 146 °C. Anal. Calcd for $C_{10}H_{11}NO_3S$: C, 53.31; H, 4.92; N, 6.22. Found: C, 52.0; H, 4.54; N, 5.94% ; IR (KBr): 2980, 1826, 1340, 1154, 1110, 1016, 908, 672, 602 cm^{-1}; ^{1}HNMR (CDCl₃): δ 2.45 (s, 3H), 4.65 (s, 4H), 7.4 (d, 2H), 7.8 (d, 2H).

3-Oximino-1-(*p*-toluenesulfonyl) azetidine 6. Compound **5** was converted to the corresponding oxime using the method of Covey *et al.*[11]. To a solution of azetidinone **5** (180 mg, 0.8 mole) and sodium acetate trihydrate (432 mg, 0.32 mole) in methanol was added portionwise with stirring solid NH₂OH.HCl (106 mg, 0.27 mole) and, the resulting mixture was heated under reflux for 2 hr. The reaction mixture was filtered and the cooled filtrate was concentrated under reduced pressure. The residue was partitioned between water and methylene chloride. The organic phase was washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulphate and finally fitered. The filtrate was concentrated *in vacuo* to give the oxime **6** in 90%

yield, m.p. 170 °C. Anal. Calcd for $C_{10}H_{12}N_2O_3S$: C, 49.79; H, 5.39; N, 11.24. Found: C, 50.26; H, 4.98; N, 11.01% ; IR (KBr): 3294, (br, s), 3044, 2934, 1598, 1461, 1340, 1166, 1112, 1022, 714, 542 cm^{-1}; ^{1}HNMR (CDCl$_3$): δ 2.44 (s, 3H), 4.5 (d, 4H), 7.35 (d, 2H), 7.75 (d, 2H).

1,3,3-Trinitroazetidine (TNAZ) 7. To a refluxing solution of oxime **6** (1 g, 4.16 mmoles) in dry methylene chloride (60 mL) was added a solution of 99% HNO$_3$ (90 mL), urea (1.37 g) and ammonium nitrate (1.05 g) in methylene chloride (60 mL). After the addition was complete, the mixture was heated under reflux for 30 minutes and then cooled toRT. The reaction mixture was poured into ice and the layers were separated. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to yield crude 1,3,3-trinitroazetidine which was purified by column chromatography on silica gel using 10% petroleum ether in ethyl acetate; yield 40%, m.p. 100-101 °C. Anal. Calcd for $C_3H_4N_4O_6$: C, 18.75; H, 2.08; N, 29.16. Found: C, 18.64; H, 1.6; N, 30.4 5; IR (KBr): 3036, 1596, 1540, 1332, 1278, 1016, 842, 762, 665 cm^{-1}; ^{1}HNMR (CDCl$_3$): δ 5.5 (s, 4H); ^{13}CNMR (CDCl$_3$+DMSO-d_6): δ 63.3 (ss, 2C), 103 (ws, 1C); EIMS (70 eV, m/z): 146, 145, 116, 99, 100, 68, 57, 56, 54, 53, 52; CIMS (CH$_4$, m/z, M.wt. 192[P]): 221 (P-C$_2$H$_5$), 193 (base peak, P+1), 188 (P+1–NO$_2$+C$_3$H$_5$), 161 (P+1–H$_2$NO), 160 (P-H$_2$NO), 158 (188-NO), 147 (P + 1 – NO$_2$), 146 (P – NO$_2$), 117 (193-NO$_2$-NO), 101 (P+1–2NO$_2$), 100 (P1–HNO$_2$-NO$_2$), 70 (P-2NO$_2$-NO), 68 (P-2HNO$_2$-NO), 56, 55, 54, 52 (azetidine ring), 46 (NO$_2$), 30 (NO).

Cautions

Reactions with 99% HNO$_3$ should be carried out behind a protective barrier as should the handling of nitroazetidines which are potentially heat and shock sensitive explosives.

Conclusion

TNAZ has been prepared in laboratory scale using *p*-toluene sulfonamide and 1,3-dihalo-2-propanol derivative as starting materials. In this synthetic route key steps involve the protection of secondary hydroxyl group by tetrahydropyranyl to effect azetidine ring closure and oxidation with iodoxybenzoic acid followed by nitrolysis methods employed for simultaneous introduction of NNO$_2$ and C (NO$_2$)$_2$ groups.

Acknowledgement

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