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Technical Notes

Diazidomethane Explosion

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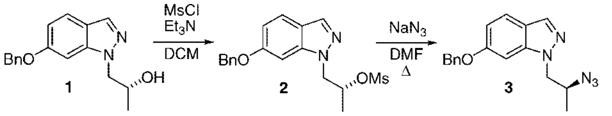
Abstract:

An explosion that caused extensive damage to a 20-L rotary evaporator and nearby equipment in a kilo laboratory was determined to have been caused by diazidomethane accumulated in the condenser. Factors contributing to this incident are discussed, and safer alternative procedures are recommended.

The explosive potential of organic azides is well-known among chemists.[1] Information on the subject can be found in standard treatises on safety,[2] but is also dispersed as part of laboratory folklore with its inherent inaccuracies. A reasonable respect for the instability of organic azides can thereby give way to both underestimation and overestimation of hazards. The latter condition, nicknamed "azidophobia," prevails in some chemical R&D environments to the extent that these versatile compounds are simply excluded as synthetic intermediates. The Sharpless group has endeavored to redress this situation by issuing useful guidelines to correlate azide structure with risk.[3a] One of the criteria set forth is that within structural categories, stability increases with the number of carbon (or comparably sized) atoms per azido group, a ratio of six or more being predictive of relative safety.[3b]

Diazidomethane, $CH_2(N_3)_2$, conversely exhibits a strong propensity to explode.[4] Fifteen years ago, the inadvertent formation of this substance by the reaction of sodium azide with dichloromethane (DCM) was implicated in laboratory explosions that typically occurred during solvent evaporation.[5,6] The danger of pairing ionic azides with polyhalomethanes has since been acknowledged, and alternative reaction media have been proposed including MeCN,[7–10] $MeNO_2$,[10,11] DME,[12] toluene,[13] acetone,[14,15] and water (with or without adjuvants).[16–18] Even so, accidents of this nature continue to happen, and their causative agent is not universally recognized.[19]

Herein we describe an explosion that occurred several years ago in the course of the reaction sequence of eq 1, which was carried out in a kilo laboratory using conventional glassware.[20]



(1)

(*R*)-1-(6-(Benzyloxy)indazol-1-yl)-2-propanol (**1**, 1.26 kg, 4.45 mol) was converted to mesylate **2** under standard conditions as indicated.[21] After an aqueous quench and phase separation the organic solution was concentrated on a rotary evaporator of 20-L capacity. The dual receiving flasks were then emptied. DMF (4 L) was added to the residue, and concentration (35 °C bath, ~20 Torr) was resumed until no further condensation was observed, the intention being to drive off DCM from the product. The residual solution of **2** was diluted with more DMF (12 L) and transferred to a reaction flask. Sodium azide (580 g, 8.9 mol) was added, and the stirred mixture was heated to 70 °C for 16 h, then cooled to rt and

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partitioned between diethyl ether and water. The organic extract was concentrated on the evaporator, and the receivers were then emptied.

The next morning it was noted that about 30 mL of a two-phase liquid had collected in the glass crosspiece at the bottom of the condenser assembly. The distilling flask containing azide **3** was disconnected and set aside in a walk-in fume hood, and the PTFE stopcock leading to one of the receivers was then opened to drain the liquid. Within seconds a loud explosion occurred. The plastic-coated condenser and receiving flasks shattered. Larger glass fragments were propelled with sufficient force to break other glassware. A 2′ square perforated metal ceiling vent cover above the evaporator was domed by pressure, while a 4 1/2′ × 8′ × 1/4″ annealed glass window panel located 20′ away was fractured by pressure or impact. Two chemists sustained noncritical lacerations but escaped more serious injury, principally by the proper wearing of safety glasses.

In the course of the investigation, crude **3** was analyzed by ^{1}H and ^{13}C NMR which revealed the presence of 8−10 mol % (i.e., 0.4 mol, 40 g) of diazidomethane.[4] The persistent hazard of residual diazidomethane became evident when a piece of a receiver assembly exploded upon being set on the metal evaporator stand, resulting in a glass cut to the investigator's hand. Therefore, the crude product **3** was subjected to hydrogenation (NH_4OCHO, EtOH, Pd(C), rt) to convert diazidomethane to nonexplosive materials.

The method used to separate DCM from mesylate **2** amounted to single-stage distillation of a solution of two components, DCM and DMF, that differ in bp by 113 °C at 1 atm. Despite this large difference in volatility, the cessation of observable condensation did not serve as a reliable signal that the evaporation of DCM was complete. A rigorous analysis of even such a canonically simple system can be challenging because of deviations from ideal behavior; qualitatively, the course of this operation can be characterized as a gradual rather than sharp decline in the ratio of DCM to DMF in the distilling flask.[22] The conditions of the subsequent azide displacement were such as to ensure conversion of any remaining DCM to diazidomethane. Then, circumstances of solvent evaporation from the product **3** evidently favored the concentration of diazidomethane beyond a critical point.[4] The presence of two liquid phases suggests codistillation with water, possibly as an azeotrope. As the evaporator stood undisturbed overnight, there was ample time for the condensate to pool and the phases to separate.

It is important to note that the complete sequence of eq 1 had been performed numerous times on smaller scale without incident. The different outcome in the present case can be attributed to unforeseen factors associated with the scale-up of evaporation. This does not imply the existence of a safe-scale threshold. The sporadic incidence of explosions under ill-defined conditions of accidental fractionation, together with extreme shock sensitivity and high explosivity, argue against the specification of any safe level of diazidomethane in a reaction extract, or of DCM or chloroform in any material input to a reaction involving azide ion. This incident highlights the potential consequences of the carry-over of DCM from one reaction to the next. The use of media other than DCM for the activation of alcohols as alkane- or arenesulfonates is the subject of ongoing research, with several alternative protocols having been reported.[23]

We conclude by noting that diazidomethane was featured in a recent summary of laboratory explosion risks directed at students and instructors.[24] We encourage all such efforts to raise and reinforce awareness of this insidious hazard.

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