A Superior Procedure for the Preparation of 2-Azetidinones From Volatile Olefins

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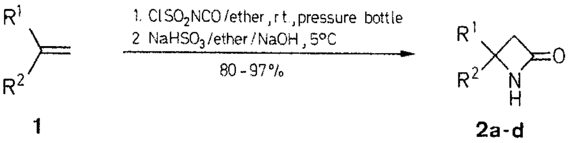
The use of a pressure bottle for cycloaddition of chlorosulfonyl isocyanate with volatile olefins not only provides the azetidinones in significantly improved yield, but also greatly simplifies the experimental procedure.

Cycloaddition of chlorosulfonyl isocyanate with olefins is a widely used general method for the preparation of azetidinones.[2] With non-volatile olefins, the reaction gives good yields of adducts, and the experimental procedures are straighforward. When volatile olefins are used, however, the yields of azetidinones range from poor to moderate,[3-6] and the reaction time can become protracted.



2	R^1	R^2
a	$H_2C{=}CH$	H
b	$H_2C{=}CH$	CH_3
c	CH_3	CH_3
d	CH_3CO_2	H

We reasoned that the poor yield of the adduct **2a**, resulting from reaction of butadiene (**1a**) with chlorosulfonyl isocyanate, was not a consequence of thermal instability of the initially formed *N*-chlorosulfonyl substituted azetidinone, but rather, stemmed from other factors. Since the cycloaddition reaction is a thermal process, the rate of reaction is retarded at low temperature. Efforts to compensate for this, by maintaining the reaction at the reflux temperature of butadiene (−5 °C) for several days result in loss af appreciable quantities of butadiene (**1a**) even with judicious temperature control.

In order to raise both the reaction temperature and prevent loss of butadiene, we conducted the reaction in a pressure bottle at room temperature. The initial adduct was not isolated, but was reduced immediately with bisulfite[7] to afford the azetidinone **2a**.[7] The yield of **2a** was 97 %, which is markedly better than the 11 and 53 % yields reported in the literature.[3,4] Cycloaddition of isobutene (**1c**) likewise produced a significantly improved yield (96 %) of the azetidinone **2c** over that reported previously.[3] Although isprene (**1b**) is not especially volatile, its cycloaddition with chlorosulfonyl isocyante was conducted under the same conditions. Again, the yield (95 %) was much better than that reported previously.[5]

We have repeatedly used the literature procedure[6] for cycloaddition of vinyl acetate **1d** and chlorosulfonyl isocyanate and have never obtained more than 25 % yield of the adduct **2d**.[8] The reaction was run several times in a pressure bottle and routinely gave the azetidinone **2d** in 90 % yield. Here, however, the reaction must be maintained at −20 °C.

In summary, the cycloaddition of volatile olefins **1** with chlorosulfonyl isocyanate in a pressure bottle, furnishes the aducts **2** in significantly increased yield (Table). Furthermore, since the reaction can be conducted at room temperature in most instances, the experimential procedure is greatly simplified.

Table. Comparative Yields of 2-Azetidinones.

Azetidinone	Lit. Yield (%)	Yield (%)	b.p. °C/torr	Lit. p.p. °C/torr
2a	11[3], 53[4]	97	80–81/1.0	81/1.0
2b	52[5]	96	70–71/1.0	70/1.0
2c	73[3]	95	63–64/0.2	62–63/0.2
2d	40–43[6]	80	-	80–82/0.001

Azetidinones 2a–2c; General Procedure:

The olefin (148 to 166 mmol) is condensed under nitrogen in a glass pressure bottle (200 ml) immersed in a dry ice-carbon tetrachloride cooling bath (−20°). Cold (−20°) ether (50 ml) and chlorosulfonyl isocyanate (14.2 g, 100 mmol) are then added. The bottle is stoppered and the cooling bath is replaced with an ice bath. The ice is allowed to melt and the reaction to come to room temperature, then stand for 2 days behind a safety shield. The bottle is chilled briefly in a cold bath (−78°),[9] and opened cautiously. The contents are poured, with ether washing, into a dry ice jacketed dropping funnel, then added dropwise to a rapidly stirred mixture of sodium bisulfite solution (150 ml, 25 %) and ether (100 ml) immersed in an ice-salt bath. The pH, as determined by litmus paper, is kept basic by periodic addition of 1 ml aliquots of sodium hydroxide solution (6 normal). When the addition is completed the layers are separated and the aqueous phase is further extracted with ether (2 × 50 ml). The combined ether extracts are dried with sodium sulfate, filtered and evaporated at reduced pressure to give the nearly pure azetidinone, which is a single component by TLC. Final purification of the product is accomplished by chromatography on florisil. The products are characterized by comparing their boiling points (Table) and their ^{1}H-NMR spectra with the values given in the literature.

4-Acetoxy-2-Azetidinone (2d):

The pressure vessel is cooled to −78 °C and ether (50 ml), chlorsulfonyl isocyanate (21.23 g, 0.15 mol) and vinyl acetate (**1d**; 14 g, 0.16 mol) are added. The reaction is warmed to −40° for two hours, then placed in a stainless steel beaker and put in a freezer at −20° for two days. Reductive cleavage of the *N*-chlorosulfonyl residue and isolation and purification of the product by chromatography on florisil are performed as described above to give **2d**; yield: 15.4 g (80 %).

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(9) The *N*-chlorosulfonyl adduct with isobutene readily crystallizes on cooling. This material is insoluble in ether and should be transferred to the dropping funnel with methylene chloride.