Highly Efficient Synthesis of Methylene cyclopropane

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Abstract: An efficient procedure for the preparation of methylene cyclopropane (3), a valuable starting material in organic synthesis, has been developed from methallyl chloride (1) and alkali metal [bis(trimethylsilyl)]amides [M(BTMSA)] (M = Na, K). The advantages of this new method are the higher yield of methylenecyclopropane up to 79% and a homogenous reaction mixture, i.e. both substrates are soluble in organic solvents such as toluene and dibutyl ether.

Key words: methylene cyclopropane, methallyl chloride, elimination

Based on a publication of Fisher and Applequist who reported the preparation of 1-methylcyclopropene (4) from 3-chloro-2-methylpropene (methallyl chloride, 1) and sodium amide in refluxing THF, we developed some years ago a synthesis of methylene cyclopropane (3) using the same starting materials but modified the solvent and the reaction conditions. With sodium amide, a mixture of 3 and 4 (80:20) was obtained in boiling Bu₂O in a maximum yield of 75% whereas potassium amide in the same boiling solvent produced 3 in 61% yield with 94% purity. The C₄H₆-hydrocarbon mixture of 3 and 4 can be isomerized into pure 3 by bubbling through a solution of t-BuOK in DMSO with only little loss. Pure 3 has also been synthesized from 1 (43%) by application of the base mixture NaN₃/t-BuONa. These syntheses suffers from some disadvantages which hinder the preparation of 3 in larger amounts. This, however, is necessary if 3 should be used as starting material in organic synthesis. The most important disadvantages are the following: 1) sodium and potassium amides are insoluble in organic solvents and must be applied as powder, which is too dangerous in technical procedures; and 2) two of the three reaction products, the C₄H₆-hydrocarbons and ammonia are gases at room temperature and must be separated in an additional step, conveniently by bubbling through an aqueous H₂SO₄ solution.

To circumvent these disadvantages we looked for soluble bases with similar or even better properties than MNH₂ and found these in the alkali metal [bis(trimethylsilyl)]amides [M(BTMSA)]. Amides 2b and 2c are strong bases with special properties. They are conveniently available also in larger amounts and are soluble in organic solvents like aromatic hydrocarbons or dialkyl ethers.

Slow addition of methallyl chloride (1) to a vigorously refluxing solution of 2b or 2c in toluene, o-xylene or dibutyl ether immediately causes a gas stream of C₄H₆-hydrocarbons 3 and 4 whose compositions and yields depend mainly on the base used, and to a minor extent on the boiling point of the solvent (Scheme). The best results are obtained with 2c (M = K) in refluxing toluene or Bu₂O that directly affords methylene cyclopropane (3) in good purity and yield (see Scheme). Amide 2b (M = Na) produces the C₄H₆-hydrocarbons in comparable yields, but 3 is now contaminated with larger amounts of 1-methylcyclopropene (4). To obtain pure 3 it is therefore necessary to isomerize 4 into 3 in a second step that is conveniently performed by bubbling the 3/4-mixture through a 50 °C warm solution of t-BuOK in DMSO. Interestingly no C₄H₆-hydrocarbons are obtained when Li(N(SiMe₃)₂)₂ (2a) is used as the base under otherwise identical conditions. This is remarkable because it is well known that strong lithium bases, e.g. LiCl (lithium disopropylamide) metalset allyl chlorides in the α-position at low temperatures. Therefore it is reasonable to assume that α-metalation takes place, but subsequent reactions other than α-elimination of LiCl, e.g. C=C-coupling, are faster.

On the other hand it has been reported that 1 reacts with two equivalents of pure, lithium bisamide-free phenyl lithium to give 1-lithium-2-methylcyclopropene in a yield as high as 60–80%. These difficulties can be circumvented by adding a second base, e.g. t-BuOK, to the reaction mixture, e.g. a 1:1 mixture of 2a and t-BuOK in toluene at 110 °C, readily liberates a 3/4-mixture in the ratio 88:12 and a yield of 73%. Addition of t-BuOK to 2b has also a beneficial effect on the yield and 3/4-ratio; e.g. from 1 and the base mixture 2b/t-BuOK in boiling Bu₂O a 3/4-mixture is obtained in the ratio 91:9 and a yield of 81%. The latter observation indicates that a metal–metal exchange occurs and the so formed 2c acts as the active base.

In summary, we have developed an efficient and simple procedure to synthesize pure 3 in large amounts.

2-Methyl-3-chloropropene (methallyl chloride, 1) was purchased from Merck KGaA and used without further purification. Amide 2a was prepared from BuLi and hexamethyldisilazane, (Merck KGaA), and 2b,c were prepared from MNH₂ and hexamethyldisilazane according to a literature procedure. The solvents THF, toluene, o-xylene and Bu₂O were dried before use. All reactions were
carried out under argon. Yield and $3/4$-ratio of the C$_4$H$_6$-hydrocarbons, as well as the purity of 3 were determined by GC (50 m OV1/3046 capillary column, N$_2$, FD, 40–260 °C, 8/min).

**Methylenecyclopropane (3) from Methallyl Chloride (1); General Procedures**

*Method 1*: With NaN(SiMe$_3$)$_2$ ($2b$)

Compound $2b$ (57.2 g, 0.31 mol) was dissolved in a solvent (THF, toluene, $o$-xylene or dibutyl ether, 100 mL) in a 250 mL three-necked flask, equipped with a 25 mL dropping funnel, water-cooled Dimroth condenser, magnetic stirrer, an argon gas bubbler and an inlet tube connected to a –80 °C cold trap. To this vigorous boiling solution was added $1$ (22.7 g, 0.25 mol) over ca. 20 min. Product 3 or a mixture of 3 and 4 that escaped from the flask through the condenser was condensed via the inlet tube in a trap at –80 °C as a colorless liquid. After an additional 30 min reflux, the reaction was over.

In THF: A mixture of 3 and 4 (GC: 80% 3 and 20% 4) was obtained from 1 (22.6 g, 0.25 mol) and 2b (57.2 g, 0.31 mol); yield: 5.9 g (8.2 mL, $d = 0.72$ g/mL, 44%).

In Toluene: A mixture of 3 and 4 (GC: 55% 3 and 45% 4) was obtained from 1 (22.6 g, 0.25 mol) and 2b (57.2 g, 0.31 mol); yield: 9.8 g (13.6 mL, 72%).

In $o$-Xylene: A mixture of 3 and 4 (GC: 76% 3, 24% 4) was obtained from 1 (25.5 g, 0.28 mol) and 2b (64.3 g, 0.38 mol); yield: 10.8 g (15.0 mL, 71%).

Method 2: With KN(SiMe$_3$)$_2$ ($2c$)

Apparatus and procedure were the same as described under Method 1. A slight excess of $2c$ ($2c = 1:1.2$) was used. The Table summarizes the results obtained in different solvents.

In THF: A mixture of 3 and 4 (GC): 61.5% toluene and 38.5% hexamethyldisilazane [calcd 355 g/mol], was obtained. 

Method 3: With Base Mixture $2a$ and $t$-BuOK: The base $2a$ (58.3 g, 0.35 mol) and $t$-BuOK (51.0 g, 0.46 mol) were dissolved in toluene (150 mL) whereby a heat evolution to ca. 40 °C was observed. The mixture was heated to a vigorous reflux ($110$ °C) and at this temperature 1 (31.6 g, 0.35 mol) was added within 45 min. Immediately C$_4$H$_6$-hydrocarbons escaped which were condensed in a –80 °C cold trap; yield: 19 mL (13.7 g, 73%); colorless liquid containing 88% 3 and 12% 4 (GC). When this procedure was carried out with a slightly molar excess of $2a$ or $t$-BuOK no C$_4$H$_6$-hydrocarbon was obtained.

Method 4: With $2b$ and $t$-BuOK: The base $2b$ (62.2 g, 9.34 mol) and $t$-BuOK (10.1 g, 0.09 mol) were dissolved in Bu$_2$O (100 mL). The mixture was heated to a vigorous reflux (ca. 130 °C) and the chloride 1 (20.8 g, 0.23 mol) was added within 30 min. The C$_4$H$_6$-hydrocarbons were condensed in a –80 °C trap: 14 mL [10.1 g, 81%, composition (GC): 90.8% 3 and 9.2% 4]. The above procedure carried out with equimolar amounts of $2b$ (48g, 0.20 mol), $t$-BuOK (22.6, 0.20 mol) and 1 (18.1 g, 0.20 mol) led to the formation of 8.8 g (82%) of 97% 3 contaminated with 3% of 4.

**Large Scale Preparation of Methylenecyclopropane (3)**

The base $2b$ (500 g, 2.73 mol) was dissolved in toluene (700 mL) in a 3 L four-necked flask, equipped with a 250 mL dropping funnel, a water-cooled Dimroth condenser, a KPG-stirrer, an argon gas bubbler and an inlet tube connected to a –80 °C cold 250 mL trap. The mixture was heated to a vigorous reflux and at this temperature 1 (199 g, 2.2 mol) was added under stirring within 4 h. From the beginning of the addition of 1, a continuous gas stream of 3 and 4 escaped via the condenser and the inlet tube, which was condensed in the trap at –80 °C. After an additional 1 h reflux, whereby a slow stream of argon transported the rest of 3 and 4 into the trap, a mixture of 3 and 4 (138 mL, $d = 1.72$ g/mL, 99.4 g; 84%, GC: 78% 3 and 22% 4) was collected as a colorless liquid.

**Table** Reaction of Methallyl Chloride (1) with $2c$

| $1$ g mol | $2c$ g | Solvent (100 mL) | C$_4$H$_6$-Hydrocarbons g | Yield (%) | $3$ | $4$
|---|---|---|---|---|---|
| 22.6 | 0.25 | 61.7 | THF | 1.2 | 0.86 | 64 | 100 | 0
| 22.6 | 0.25 | 61.7 | $o$-xylene | 12.0 | 8.6 | 64 | 96 | 4
| 25.3 | 0.28 | 67.6 | toluene | 13.0 | 9.4 | 70 | 96 | 4

In Bu$_2$O: A mixture of 3 and 4 (GC: 85.8% 3 and 14.2% 4) was obtained from 1 (22.6 g, 0.25 mol) and 2b (57.2 g, 0.31 mol); yield: 9.9 g (13.8 mL, $d = 0.72$ g/mL, 73%).

In Toluene: A mixture of 3 and 4 (GC: 55% 3 and 45% 4) was obtained from 1 (22.6 g, 0.25 mol) and 2b (57.2 g, 0.31 mol); yield: 9.8 g (13.6 mL, 72%).
The remaining residue (275 g) was a white powder. The above described procedure carried out with 1 (390 g, 4.3 mol) and 2b (791 g, 4.3 mol) in Bu₂O (1.5 L) led to the formation of 199 g (77%) of C₄H₆-hydrocarbons with the composition (GC): 91.6% 3 and 8.4% 4.

**Pure Methylene cyclopropane (3)**
A mixture of 3 and 4 (138 mL, 99.4 g, 1.84 mol) was bubbled through a solution of t-BuOK (9.8 g, 88 mmol) in DMSO (60 mL) at 50 °C and recondensed in a ~80 °C flask. The resulting 3 (130 g, 94%) was 99.4% pure (GC).

**References**

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