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Phosgenation reactions with phosgene from triphosgene

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KEYWORDS

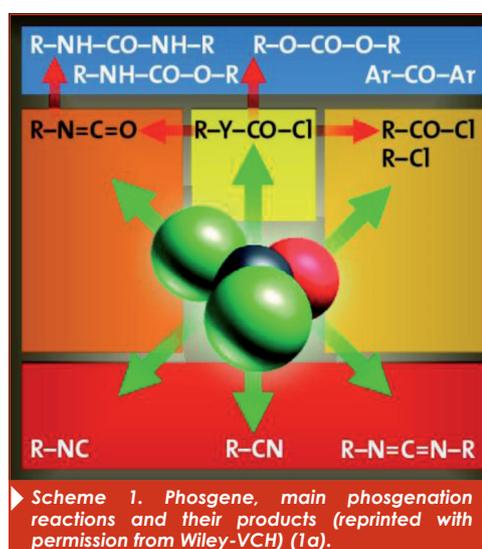
Phosgene, Triphosgene, Phosgenation, Phosgene Generator, Cartridge Phosgenation, Solid Phosgene, BTC

ABSTRACT

Presented is a method to combine advantageous properties of both phosgene and triphosgene (solid phosgene, BTC) in a two-step process for typical phosgenation reactions to form chloro-carbonates and isocyanates. Also a 5 kg triphosgene batch process for the synthesis of benzyl chloroformate within a loop reactor is documented. Scope and limitations of these triphosgene applications are discussed. A concept for a small-scale batch processing phosgene generator ready for construction is presented.

INTRODUCTION

Performing organic syntheses phosgene is an essential and often indispensable reagent (1) used nowadays in about 20,000,000 tons a year worldwide. Main phosgenation reactions and their versatile products are shown in Scheme 1 and Table 1. Only four atoms effect the four transformations chloro-carbonylation, carbonylation, chlorination, and dehydration forming the products chloro-carbonates, carbamoyl chlorides, isocyanates, carbamates, ureas, carbonates, diaryl ketones, alkyl chlorides, acyl chlorides, nitriles, isocyanides, carbodiimides, and anhydrides (1a). For the high toxicity of phosgene, many safer procedures and substitutes for phosgene have been developed, which have been extensively discussed in (1a). The only real equivalents of phosgene are diphosgene and triphosgene (solid phosgene, BTC), at which triphosgene is much more stable than diphosgene. The adequate literature on phosgene and triphosgene as well as on 70 phosgene substitutes up to 2002 has been presented extensively in (1a). A new issue of the phosgene chapter in Kirk-Othmer has been presented (1b) and problems with syntheses of phosgene and their solution were treated (1c). Methods for the transformation of triphosgene into phosgene have been developed (2), but only one solvent-less process has been presented (2a, b, e).



Many papers on the synthetic applications of triphosgene have been published (3e-j), under these an improved process for biotin (3j).

More interest gains carbon dioxide as a phosgene substitute (4). In the analytical class new tests for phosgene and triphosgene (5) have been developed.

The inhalation exposures of rats with phosgene, diphosgene, and triphosgene have been investigated (6).

The scope and limitations of a reasonable application of triphosgene generating phosgene will be discussed.

Phosgenation reaction	Starting materials	Products		
Chloro-carbonylation	alcohol	R-OH	chloro-carbonate	R-O-CO-Cl
	sec. amine	R ₂ NH	carbamoyl chloride	R ₂ N-CO-Cl
	alcohols	2 R-OH	carbonate	R-O-CO-O-R
	amines	R-NH ₂	isocyanate	R-N=CO
Carbonylation	amines	2 R-NH ₂	urea	R-NH-CO-NH-R
	alcohol, amine	R-OH, R-NH ₂	carbamate	R-O-CO-NH-R
	arenes	2 ArH	diaryl ketone	Ar-CO-Ar
Chlorination	alcohol	R-OH	alkyl chloride	R-Cl
	carboxylic acid	R-CO ₂ H	acyl chloride	R-CO-Cl
Dehydration	carboxamide	R-CO-NH ₂	cyanide	R-CN
	formamide	R-NH-CHO	isocyanide	R-NC
	urea	R-NH-CO-NH-R	carbodiimide	R-N=C=N-R
	carboxylic acid	R-CO ₂ H	anhydride	R-CO-O-CO-R

► **Table 1.** Main phosgenation reactions and their products (1a).

PHOSGENE VERSUS TRIPHOSGENE AND COMBINING THEIR PROPERTIES

To evaluate the phosgenation reagents both triphosgene and phosgene, their physical and chemical properties as well as their thermochemical and toxicity data are compared in Table 2. There you can see, that both reagents have important advantages, but also disadvantages.

Data	Phosg.	Triphos.	Lit.
m.p. (°C)	-118	80	1a
b.p. (°C)	8	206	1a
Vapor pressure (Pa) at 20 °C (mm Hg)	162,000 1,215	20 0.15	1a
rel. Reactivity to MeOH	170	1	3d
$\Delta H_{\text{transformation}}$ (J g ⁻¹)	-	+9	2a
$\Delta H_{\text{decomposition}}$ (J g ⁻¹)	-	-243	2a
Toxicity, LC ₅₀ (mg m ⁻³) (mmol m ⁻³)	7 0.07	41.5 0.14	6

Table 2. Physical, chemical, thermochemical, and Toxicity data of phosgene and triphosgene.

High melting and boiling points as well as low volatility (vapour pressure at r.t. 8,000 times lower than of phosgene) make triphosgene appropriate for its transport and storage, also loading of small amounts by simple weighing, down to milligrams. Loading of huge amounts of the solid triphosgene is rather complex. Also, these properties make triphosgene partially difficult to be removed from reaction mixtures, for a detailed consideration look at (2a).

As a gas, however, phosgene can be easily loaded as well as removed by simple stripping or distillation.

Only small quantities are difficult to load. Phosgene is about 170 times more reactive than triphosgene in the reaction with methanol. Regarding toxicities triphosgene has a higher LC₅₀ than phosgene, for further considerations on toxicity look at (6). It is obviously that both phosgenation reagents have specific advantages, and we need not to decide for one or the other. But we can utilise the combined advantages and avoid disadvantages. In such a great market as that of phosgene, user profiles are entirely different. Roughly one can observe three consumer profiles:

1. The million tons markets of polymers as are polyurethanes and polycarbonates, which yet need nearly solely phosgene. They are best equipped to it in special facilities.
2. The pharma and fine chemicals markets and kilo-labs, which are often not adequately equipped to produce or store phosgene in greater amounts. Often the chemists do not like bottles and bombs of phosgen or chlorine and carbon monoxide standing around in the laboratories.
3. The lots of research chemists, who need sometimes only several grams of phosgene and mostly can replace it by triphosgene or other phosgene substitutes (1a). But several reactions or procedures run only or only good by use of phosgene.

We will see a noticeable demand of group 2 and a moderate one of group 3 for a simple, safe, and occasional access to phosgene in defined quantity without its storage. *I.e.*, one can run a phosgenation reaction at any time, where phosgene is generated in a rate as it will be consumed.

This is now possible by use of the solventless and safe process for the quantitative production of phosgene from triphosgene (2a).

THERMAL STABILITY AND PURITY OF TRIPHOSGENE

A crucial part of this safety concept is the thermal stability of triphosgene. In 1999 (3c) DSC (differential scan calorimeter) measurements provided an onset of decomposition at 160°C with an enthalpy of -200 J g⁻¹. But recent DSC measurement of commercially available triphosgene (Aldrich) at the company Dynamit Nobel GmbH, resulted in the complete stability of pure triphosgene up to 200°C. The DSCs have been run in a hermetic closed crucible of glass up to 350°C with a temperature gradient of 10, 5, 3 and 2 K min⁻¹ (Figure 1). In all runs the onsets of the decompositions were above 200°C (201-204°C), decomposition enthalpies were -132 to -243 J g⁻¹. Thus the thermal decomposition of triphosgene is moderately exothermic and the shape of the waves show, that there is no thermal runaway reaction.

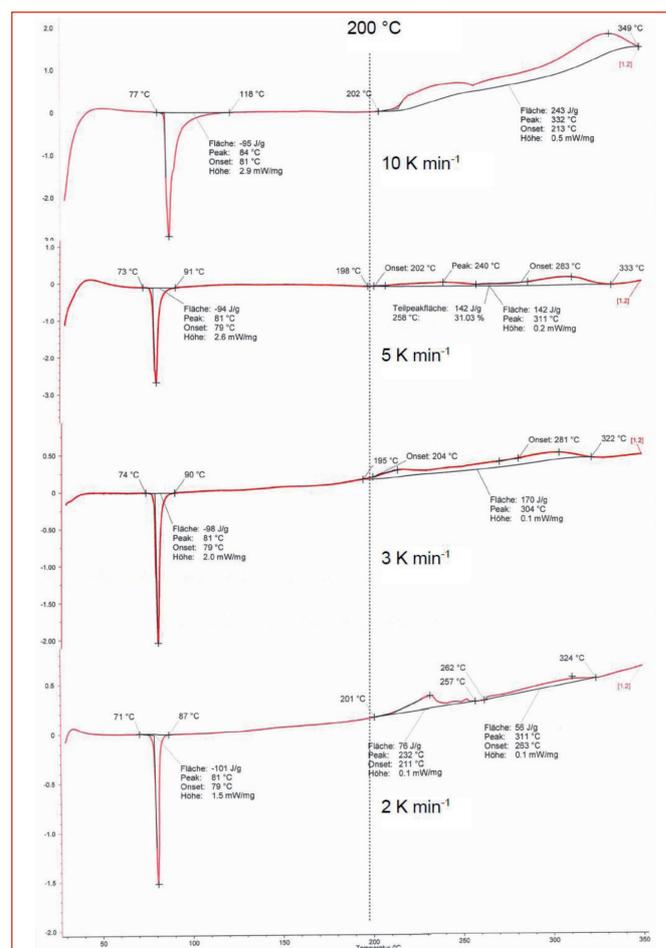
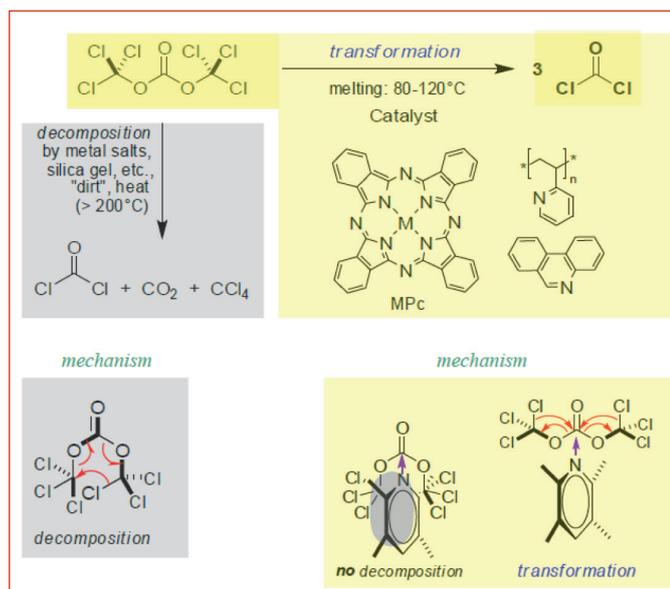


Figure 1. Four DSC runs of triphosgene with temperature accelerations of 10, 5, 3, and 2 K min⁻¹.

Pure triphosgene is the precondition of all expedient work with it and is required for the following process. Not completely chlorinated species of triphosgene are liquid and much less stable. Triphosgene can be easily proved by NMR spectroscopy in CDCl₃, which takes only time of 5-10 min. Chemical shifts of the triphosgene peaks in ¹³C-NMR are δ 108.0 and 140.9 ppm, the pattern is very significant. The ¹H-NMR spectrum must not at all show any signal. The triphosgene must be free of metal salts.

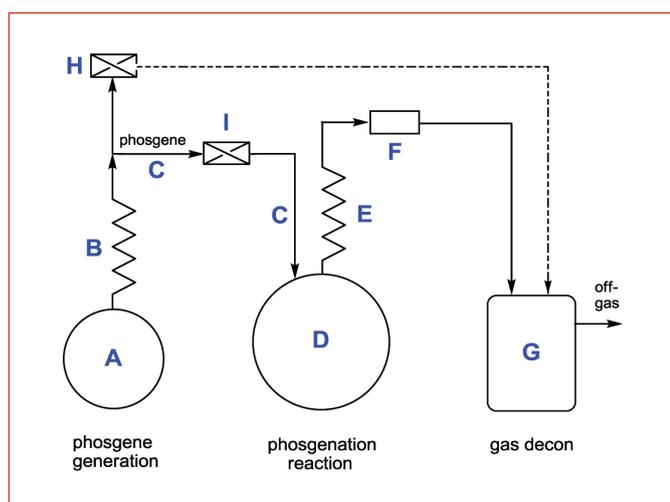
SAFE AND SOLVENTLESS PROCESS TO PRODUCE PHOSGENE FROM TRIPHOSGENE

The safe process is described in detail in (2a), it transforms quantitatively triphosgene into phosgene without any solvent, the reaction is controlled thermally and by the catalyst concentration (Scheme 2).



► **Scheme 2. Thermal conversion of triphosgene along two ways: decomposition or transformation (2a).**

So it can be adjusted to the following phosgenation reaction. This phosgene is free of triphosgene. Triphosgene sublimes initially in the transformation process (Scheme 3) to the condenser (B), but it gets washed back from (B) into the vessel (A) by intermediately generated liquid diphosgene, which has been carried away by the flow of phosgene (2a).



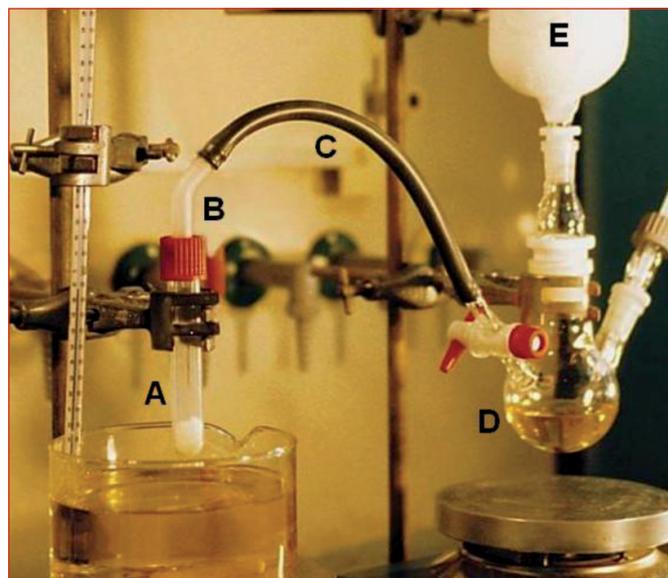
► **Scheme 3. Process Flow Diagram (PFD) of the Safety Phosgenation.**

(A) Phosgene generator, filled with triphosgene and the catalyst.
(B) Reflux condenser (water cooled, T=15°C), (C) Phosgene line (Viton hose),
(D) Phosgenation reaction vessel, (E) Reflux condenser (T= -20 to -78°C),
(F) Drying-tube, (G) Scrubber for the off-gas,
(H) Pressure relief valve, (I) non-return valve.

We performed phosgenation reactions using phosgene from triphosgene in a scope of 1g to 5 kg. There are 0.02 and 0.05 mol phosgenation cartridges commercially available (7), filled with 2 or 5 grams of triphosgene and a capsuled special catalyst. An adapter belongs to the kit with viton hose to connect the cartridge to the phosgenation vessel (Figure 2). A dosimeter badge to be fixed at participating persons to measure possible phosgene contaminations in the atmosphere is attached to the package.

PHOSGENATION REACTIONS

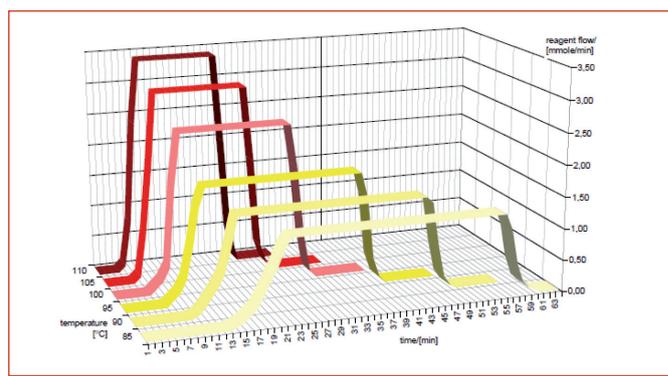
To achieve a minimum of actual existing phosgene in the whole equipment for a phosgenation reaction (Scheme 3), it is



► **Figure 2. Micro-unit phosgenation equipment.**
(A) Cartridge for Safe Phosgenation. (B) Adapter.
(C) Viton hose. (D) Phosgenation reaction vessel.
(E) Dry-ice reflux condenser.

necessary to adjust the reaction rate of the phosgene generation to the reaction rate of the phosgenation reaction. For practical purposes we determine in a small scale process the reaction time by analysing the reaction mixture of the phosgenation reaction with NMR- or IR-measurements or other adequate analytical methods. Then we choose an appropriate rate of phosgene generation. It can be the same rate as of the phosgenation reaction, but it can also alter from this. But it has to be reasonable, for the choice of a rate depends on the understanding of the phosgenation reaction by an experienced chemist in this field. For micro-units the phosgene generator (A) in Scheme 3 will be replaced by the above mentioned standardised phosgenation cartridges to produce 0.02 or 0.05 mol of phosgene (7) according to Figure 2.

For these cartridges the three-dimensional Figure 3 presents the kinetics of the phosgene flow and its duration dependent on the heating temperature of 85 to 110°C in steps of 5°C each. At all temperatures the reactions end sharply. Thus, reaction times can be determined precisely.



► **Figure 3. Reaction flow and time for 6 varying temperatures for the 0.05 mol Cartridge for Safety Phosgenation. The delay of 4 - 12 min at the beginning of heating is caused by the melting phase of triphosgene.**

METHYL 2-ISOCYANATO 2-METHYLPROPIONATE USING THE 0.05 MOL CARTRIDGE FOR SAFETY PHOSGENATION (7)

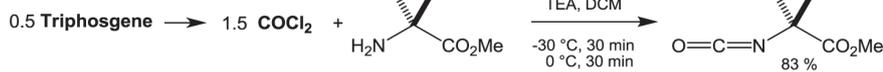
Procedure

According to Scheme 4 and Figure 2. A 250 ml four-necked flask (D) with gas-inlet, inner thermometer, dropping funnel, magnetic

**ATTENTION!**

By working with phosgene, triphosgene, isocyanates, and chloroformates, necessarily respect the instructions in (2a) and many advices in the relevant literature as (1a) as well as the recent safety data sheets and the instructions of your institution! All these chemicals are very toxic (T*) and have to be handled in an anhydrous atmosphere in a hood with a strong exhauster!

Four case studies applying different consumptions of phosgene (0.05 mol, 1 mol, 50 mol) on phosgenation reactions and phosgene production (300 mol h⁻¹) from triphosgene are presented below.



Scheme 4. Reaction of methyl 2-amino 2-propyl -propionate with phosgene.

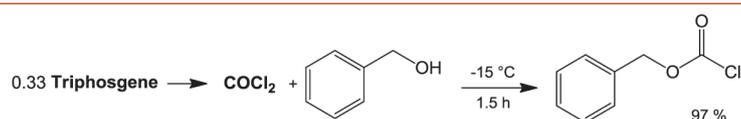
stirrer, and dry-ice cooled reflux condenser with gas-outlet, which is connected to an off-gas-line ending in the exhauster suction hole of the hood. The flask is pre-charged with dichloromethane (20 ml) and cooled to -50°C by a dry-ice cooling bath. Then a 0.05 mol Phosgenation Cartridge (A) (7) is connected to the above 250 ml flask (D) with the adapter and hose and heated by an oilbath at 110°C. The tap of the gas-inlet must be open. After 4 min all triphosgene is molten and a constant evolution of phosgene takes place, ceasing rather abruptly after 19 min. Thereby the temperature in the flask (D) rises to -30°C. Now the gas-inlet tap is closed and the cartridge (A) separated (8). Methyl 2-amino 2-methylpropionate hydrochloride (5.2 g, 0.033 mol) is added to the flask (D) and vigorously stirred. Triethylamine (14 ml, 0.1 mol) dissolved in dichloromethane (20 ml) is dropped to the mixture within 30 min at -25 to -30°C inner flask temperature. Then the reaction mixture is allowed (under stirring) to come over 30 min to 0°C and stirred a further 30 min at 0°C. Then pentane (40 ml) is dropped under stirring to the mixture in 5 min and the mixture is allowed to stand for further 30 min. The precipitation is filtered off, the precipitate washed with pentane (a few ml) and the combined liquid phases are concentrated *in vacuo*. The residue is macerated in pentane (10 ml) and layed for 3 days into the refrigerator at about 0°C. Filtering off the precipitate, concentrating of the filtrate and drying the residue *in vacuo* provides a nearly colourless liquid of pure methyl 2-isocyanato 2-methylpropionate (3.94 g; 83 percent). IR (neat): 2250 (NCO), 1730 (CO) cm⁻¹. ¹H-NMR (CDCl₃): 1.35 (s, 6 H), 3.30 (s, 3 H).

BENZYL CHLOROFORMATE, 1 MOL

Pure benzyl chloroformate free of dibenzyl carbonate and benzyl chloride has been prepared in 97 percent yield (Scheme 5), when pre-charged phosgene and benzyl alcohol react at low temperatures of -10 to -20°C (1a).

Procedure

(1a): According to Scheme 3. A 250 ml round bottomed flask (A) with a magnetic stirrer is charged with triphosgene (100 g, 0.337 mol) and catalyst phenanthridine (120 mg, 0.67 mmol) (2a) and heated at 110°C oil bath temperature. After 11 min all triphosgene is molten and a constant phosgene flow takes place, which is



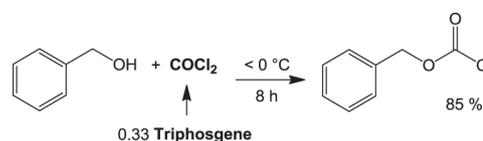
Scheme 5. Reaction of benzyl alcohol with phosgene (1 mol).

condensed in a three-necked 1 l round bottomed flask (D) with magnetic stirrer, gas inlet, dry-ice cooled reflux condenser with gas outlet (HCl) to a scrubber, and inner thermometer, cooled by a dry-ice / ethanol bath at -50°C. After 21 min the gas evolution ceases. Flask (A) is separated and cleaned up according to (8). Then the gas-inlet of flask (D) is exchanged by a dropping funnel and benzyl alcohol (108 g, 1.00 mol) is added dropwise at -10 to -20°C in 1.5 h. The reaction mixture is stirred 12 h at 0°C (ice bath) while reaction controlling by TLC. Then the cooling bath is exchanged by an oil bath and the tops on the flask are exchanged by a distillation apparatus. The crude chloroformate is distilled *in vacuo* affording 165.1 g (97 percent) of colourless

benzyl chloroformate, bp 41°C (0.03 Torr), Analyses (¹H-, ¹³C-NMR, IR, TLC) show a pure product (without any benzyl chloride or dibenzyl carbonate).

BENZYL CHLOROFORMATE (Z-CL), 50 MOL, USING A LOOP REACTOR

On the other hand for security reasons the actual existing phosgene should be a minimum, so the process should run reverse with pre-



Scheme 6. Reaction of benzyl alcohol with phosgene (50 mol).

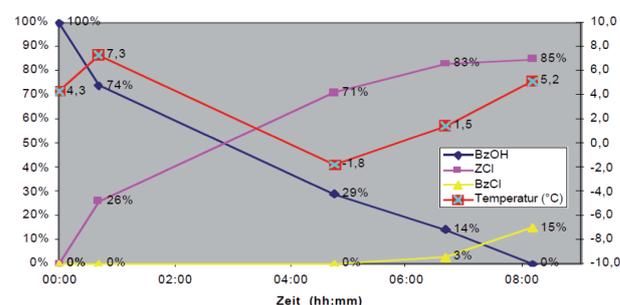


Figure 4. Reaction data of the loop reactor: Concentrations of benzyl chloroformate, benzyl alcohol and benzyl chloride as well as temperature versus time.

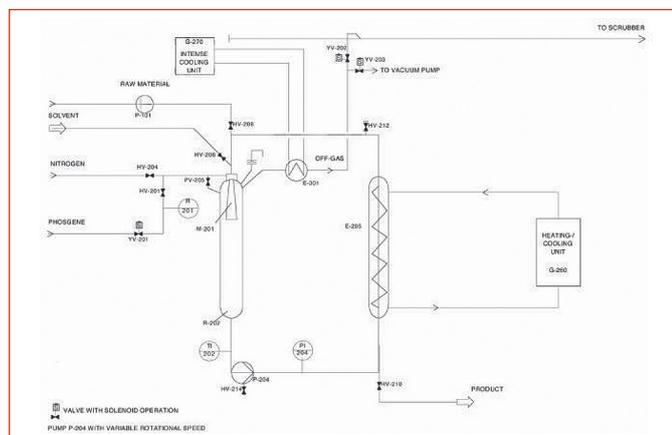
charged benzyl alcohol and adding phosgene (Scheme 6) in a loop reactor (Scheme 7 and Figure 5) (9), where the reactants are intensively mixed. Thus, a 100 percent selectivity of the reaction could be achieved, no dibenzyl carbonate has been observed. Due to an increase of reaction temperature (10) after 5 h some benzyl chloroformate decomposed to form 15 percent benzyl chloride, yield of benzyl chloroformate was 85 percent (Figure 4).



Figure 5. Loop reactor of Buss Chem Tech (9).

Procedure

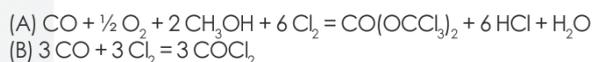
According to Schemes 3, 7 and Figure 5. (A) Triphosgene (4.9 kg, 16.5 mol), catalyst α -copper phthalocyanine α - CuPc (5 g, 8 mmol) (2a), reaction temperature 85°C, reaction time 6.5 h. (D) Loop reactor (Figure 5): Benzyl alcohol (5.2 kg, 48 mol), Reaction temperature -2 to 5°C, reaction time 8 h, reaction control by $^1\text{H-NMR}$, yield of benzyl chloroformate is 85 percent.



Scheme 7. Experimental setup of the reaction with the loop reactor.

SCOPE AND LIMITATIONS

1. Because the process of catalytic transformation of triphosgene to phosgene (Scheme 2) has no heat of reaction ($\Delta H = +9 \text{ J g}^{-1}$, Table 2), there is in principle no limitation in up-scaling the process from the thermochemical point of view. The required purity of triphosgene can easily be checked by NMR-spectroscopic analyses (see above) to exclude a potential thermal decomposition of triphosgene (Scheme 2).
2. Both gaseous phosgene and solid triphosgene are very toxic (T^+) and require special precautions as gas or as solid, respectively.
3. As phosgene and triphosgene are applied in similar syntheses, the ecological considerations on both processes will be focussed on the atomic balance for the production of triphosgene (A) and "classic" phosgene production (B) (Scheme 8). (A) needs twice the amount of chlorine and delivers hydrogen chloride, not so the "classic" phosgene processes (B). This is crucial for huge phosgene productions as the million tons market.



Scheme 8. Atomic balance of triphosgene production (A) and the "classic" phosgene production (B).

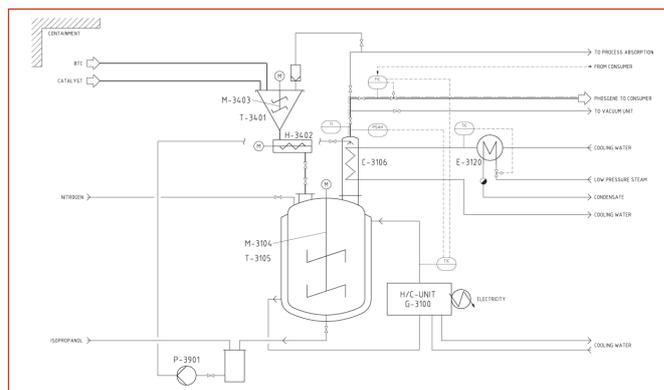
4. Comparing both production processes from above, economical overall calculations result in a price advantage of the triphosgene process up to 30 kg h^{-1} phosgene production.

Facit

The presented process is a typical small-scale process.

SMALL-SCALE PHOSGENE GENERATOR FOR THE PRODUCTION OF 30 KG H^{-1} , 300 MOL H^{-1} , PHOSGENE

The above considerations led to provide the phogene market with a new production unit. A Small Scale Phosgene Generator (Scheme 9 and Figure 6) with an operating Volume of 50 l and a maximum phosgene flow of 30 kg h^{-1} has been designed ready for construction by Buss Chem Tech AG (9).

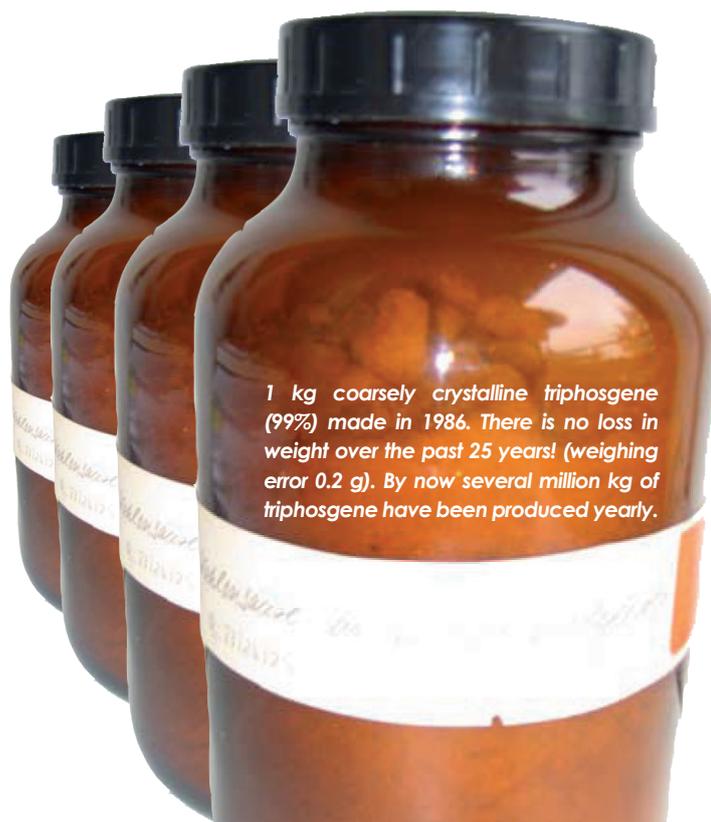


Scheme 9. Basic diagram Phosgene Generator from Buss Chem Tech (9).



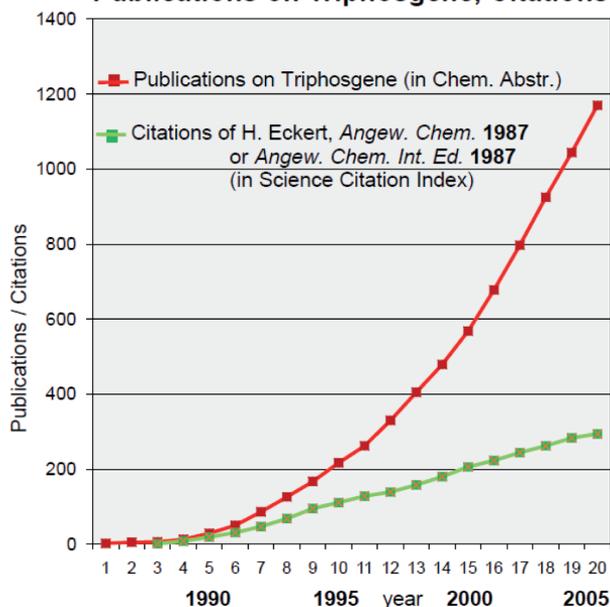
Figure 6. Phosgene Generator layout.

Further data: Temperature 150°C; according GMP guidelines; electric energy 0.45 kW/kg phosgene; EEx classification: equipment class 3G, temperature class T3, explosion group IIB.



1 kg coarsely crystalline triphosgene (99%) made in 1986. There is no loss in weight over the past 25 years! (weighing error 0.2 g). By now several million kg of triphosgene have been produced yearly.

Publications on Triphosgene, Citations



Publications on triphosgene and citations of the author in 1986 – 2005.

CONCLUSIONS

The presented process utilises advantages and avoids disadvantages of both phosgene and triphosgene properties by a two-step process. Solid triphosgene can easily be transported and stored. The produced gas phosgene from it can easily be charged and removed. This makes working with phosgene from triphosgene efficient in typical small-scale processes. In these the new method may be even more cost efficient than the classical methods. Scope of the process is the gram up to kg range, from micro-units up to semi-technical devices. Finally the market will decide this.

ACKNOWLEDGEMENTS

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- Sigma Aldrich, Starter Kit (1 Cartridge for Safe Phosgenation 0.02 mol, 1 gastight adapter with hose, 1 dosimeter badge + paper, instructions) **519782**; Replacement Cartridges 0.02 mol **519758** and 0.05 mol **519766**.
- The cartridge and hose are fully filled with ethanol, which can be disposed of as chlorinated organic waste solvent 10 min later. The cartridge can be disposed of as solid waste. The phosgene resistant adapter and tubing can be often reused.
- Buss Chem Tech AG, Hohenrainstr. 12a, CH-4133 Pratteln, Switzerland, info@buss-ct.com.
- The cooling unit was not efficient enough to hold the temperature at the rated value.

Special mini-unit phosgenation equipment. Right side: Cartridge for the safe generation of phosgene from 1–5 g of triphosgene over a heating oil-bath. Middle: Reaction vessel including a filter plate joined to a flask (left) and a balloon (right) filled with argon over an ultrasound bath charged with ethanol, which can be cooled by dry-ice. This device allows running the phosgenation reaction and filtering the reaction mixture in a sole unit and thus avoids the release of phosgene.