|  |  |
| --- | --- |
| **TILE TP.3**  **Production of (1-Bromocyclopentyl)-2-thienyl ketone (IP.2)** | |
| Process started at:  \_ \_ . \_ \_ . \_ \_ \_ \_ \_ \_ : \_ \_  Date Time | Production Manager:  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_  Name Signature |
| Process finished at:  \_ \_ . \_ \_ . \_ \_ \_ \_ \_ \_ : \_ \_  Date Time | Production Manager:  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_  Name Signature |

|  |  |
| --- | --- |
| **REFERENCES:** | |
| Development Report: | MDDR 201909 TILE (current version) |
| Validation Plan: | QDVR 202001 TILE (current version) |
| Technological Chart: | MD-TC 257-2 (current version) |
| Cleaning Instruction: | MD-CI TILE (current version) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PROCESS OPERATORS:** | | | | |
| **No** | **Name** | **Surname** | **Responsibilities** | **Signature** |
| 1 | Denys | Verves | Production Manager |  |
| 2 | Ivan | Ogibalov | Deputy of Production Manager |  |
| 3 |  |  | Operator |  |
| 4 |  |  | Operator |  |
| 5 |  |  | Operator |  |
| 6 |  |  | Operator |  |

| **TABLE 1.1 – LOADED MATERIALS** | | | | | |
| --- | --- | --- | --- | --- | --- |
| Material | Warehouse code | Important quality/other attributes | Theoretical calculated amount per 1 kg of starting material [kg] | Amounts for this batch | |
| **Specified loading  (range) [kg]** | **Actual loading**  **[kg]** |
| **Cyclopentyl 2-thienyl ketone, purified (TILE IP.1, purified)**  (Op. 7)  **(Starting material of this TP)** | (Example: TBD-9322-X IP.1 purified) | Total impurities NMT 5.0 % | 1 kg | **Min-max loading 5-10 kg**  9.80 kg  ( 9.75 - 9.85 kg) |  |
| **Copper (II)bromide (CuBr2)** (Op.5) | (Example: CuBr2 XXX) | Assay (as Cu)  NLT 27.0 % | 2.70 ± 0.05 kg | 26.46 kg  ( 26.06 - 26.86 kg) |  |
| **Methanol** | (Example: MARO MEOH XXX) | Assay NLT 99.0 %  d=0.792 g/mL | For reaction, Op.3 | | |
| 3.40 ± 0.2 kg | 33.32 kg  ( 33.12 - 33.52 kg) |  |
| For rinsing the reactor from reaction mixture, Op. 19 | | |
| Fixed amount | 3.60 ± 0.2 kg |  |
| For rinsing precipitate, Op. 20 | | |
| Fixed amount | 3.60 ± 0.2 kg |  |
| For rinsing the reactor in the end of interim cleaning, Op. 21 | | |
| Fixed amount | 0.8 ± 0.2 kg | **(do not include into total loaded calculation)** |
| **Water for production (Water PR)** | (Example:  013-XX dd/mm/yy HH:MM) | <100 µS/cm | Total amount for process | | |
| Minimal amount  ~4.40 kg | 43.12 kg  ( 42.12 - 44.12 kg) | **(do not include into total loaded calculation)** |
| For extraction, Op.35 | | |
| 3.30 ± 0.3 kg | 32.34 kg  ( 32.04 - 32.64 kg) |  |
| **n-heptane** | (Example: HEPTANE XXX or HEPTANE95 XXX)) | Assay NLT 99%  d = 0.689 g/mL | For 1st extraction, Op. 36 | | |
| 2.7 ± 0.2 kg | 26.46 kg  ( 26.26 - 26.66 kg) |  |
| For 2nd extraction, Op. 42 | | |
| 1.0 ± 0.2 kg | 9.80 kg  ( 9.60 - 10.00 kg) |  |
| **Anhydrous ethanol** | (Example: EtOH abs XXX) | Assay NLT 99.5 %  d = 0.789 g/mL | For crystallization, Op.60 | | |
| 0.79 ± 0.1 kg | 7.74 kg  ( 7.64 - 7.84 kg) |  |
| For rinsing the reactor and precipitate, Op.69 | | |
| 1.20 ± 0.1 kg | 11.76 kg  ( 11.66 - 11.86 kg) |  |
|  |  |
|  | | SPECIFIED loadings are inserted to Table1 and to relevant operations by PM: | | PM’s signature:  date: |  |
|  |  |
|  |  |  | **ACTUAL loadings**  **TOTAL** loaded amount: | | \_\_\_\_\_\_\_\_\_ kg  **Operator’s** signature: |
|  |  |
|  |  | | **ACTUAL loadings**  All loadings are in specified range? | | ⬜ Yes ⬜ No  **PM’s** signature: |

| **TABLE 1.1 – PREPARATION OF NaOH SOLUTION FOR SCRUBBER** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Material | Warehouse code | Important quality/other attributes | Theoretical calculated amount per 1 kg of starting material [kg] | Amounts for this batch | | |
| **Specified loading  (range) [kg]** | **Actual loading**  **[kg]** | **Operator’s signature** |
| ⬜ **Sufficient amount of solution is available** (cross out fields below)  **Preparation performed in Batch Record of: TBD-\_\_\_\_\_\_\_\_\_\_\_\_\_ \_ \_ . \_ \_ . \_ \_ \_ \_**  pH of available solution must be checked with pH paper and recorded: …….. Requirement: pH is >12;  ⬜ **Preparation:** Water for production is measured (by volume) using water and loaded into the scrubber. Pump is turned ON and required amount of NaOH is weighed on balance 007-44 and loaded into the scrubber using a jug “Tile reagents” and a shovel “NaOH”. The solution is circulated for at least 15min before starting to use it. | | | | | |  |
| **Sodium hydroxide (NaOH)** | (Example: MARO NaOH XXX) | Assay NLT 98% | 1.0 ± 0.5 kg | 9.80 kg  (9.30 - 10.30 kg) | **(do not include into total loaded calculation)** |  |
| **Water for production (Water PR)** | (Example: 013-XX dd/mm/yy HH:MM) | <100 µS/cm | Fixed amount | 100.0 - 120.0 kg | **(do not include into total loaded calculation)** |  |
| **Preparation date, time:** | | | | **\_ \_ . \_ \_ . \_ \_ \_ \_** \_\_\_\_ : \_\_\_\_ | |  |

|  |  |
| --- | --- |
| **TABLE 2 – BEFORE STARTING THE WORK** | **Operator’s signature** |
| Room 257-2 is clean and ready for work. |  |
| Ventilation in room 257-2 is turned on and operational. |  |
| Necessary personal protective devices are present and operational.  ⬜ coats  ⬜ gloves  ⬜ protective glasses  ⬜ full face masks/respirators |  |
| Fire protection equipment is present. |  |
| Solvents and solutions for equipment and glassware cleaning are present:  ⬜ Acetone for cleaning  ⬜ DCM  ⬜ RO water, e.g. from 013-16  ⬜ 5 % aq. HCl or the components for its preparation:  conc. HCl warehouse code ……………………………………… |  |

| **TABLE 3.1 – EQUIPMENT CHECK-LIST** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Name** | **Equipment code** | **Clean and available in production room before use** | **Cleaned and visually clean at the end of work** | **Equipment logbook is filled** | **Cleaning sample needed (marked by PM)** |
| **MAIN EQUIPMENT** | | | | | |
| 100 L reactor   * stirrer * stirrer drive 021-30 * reflux condenser * overpressure release valve * liquid addition system * 20L receiver | 002-17 | ⬜ | ⬜ | ⬜ | **Yes** ⬜ **No** ⬜ |
| Heating/cooling circulator, HTF – Syltherm XLT | 011-22 | ⬜ | ⬜ | N/A | N/A |
| Nutsche filter | 046-5 | ⬜ | ⬜ | ⬜ | **Yes** ⬜ **No** ⬜ |
| Membrane pump with controller | ⬜ 001-22 or analogue  ⬜ 001-…. | ⬜ | ⬜ | N/A | N/A |
| Scrubber | 053-1 | ⬜ | ⬜ | N/A | N/A |
| Peristaltic pump | ⬜ 001-13 or analogue  ⬜ 001-…. | ⬜ | ⬜ | N/A | N/A |
| Drying oven | 012-13 | ⬜ | ⬜ | ⬜ | **Yes** ⬜ **No** ⬜ |

| **TABLE 3.2 – EQUIPMENT REQUIRING CALIBRATION CHECK-LIST** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Name** | **Equipment code** | **Precision class/**  **calibration range** | **Next calibration date (MM.YYYY)** | **Clean and available in production room before use** | **Cleaned and visually clean at the end of work** |
| **BALANCES** | | | | | |
| Balance (max 2.0 kg) | 007-10 | ±0.01 g | **\_ \_ . \_ \_ \_ \_**  Metrosert | ⬜ | ⬜ |
| Balances (max 120 kg) | 007-44 | ±10.0 g | **\_ \_ . \_ \_ \_ \_**  Metrosert | ⬜ | ⬜ |
| **THERMOMETERS/THERMOSENSORS** | | | | | |
| Thermosensor | 003-209 | -20 … +140 ⁰C | **\_ \_ . \_ \_ \_ \_** | ⬜ | ⬜ |

| **TABLE 3.3 – OTHER APPARATUS CHECK-LIST** | | | | |
| --- | --- | --- | --- | --- |
| **Name** | **Size** | **Label** | **Clean and available in production room before use** | **Cleaned and visually clean at the end of work** |
| **BARRELS/CANISTERS** | | | | |
| Canister | 10 L | 5 % aq HCl for cleaning | ⬜ | ⬜ |
| Canister(s) | 25 L | Organic waste | ⬜ | N/A |
| Canister(s) | 25 L | Crystallization mother liquor | ⬜ | N/A |
| Barrel | 200 L | Aqueous waste | ⬜ | N/A |
| **UTENSILS** | | | | |
| Jug | 2 x 5L | Tile solvents | ⬜ | ⬜ |
| Jug | 5L | Tile reagents | ⬜ | ⬜ |
| Jug | 5L | 266 cleaning | ⬜ | ⬜ |
| Jug | 5 L | TILE TP.3 | ⬜ | ⬜ |
| Jug | 1 L | MeOH | ⬜ | ⬜ |
| Funnel | N/A | AQ. SOLUTIONS | ⬜ | ⬜ |
| Funnel | N/A | TILE TP.3 reactor | ⬜ | ⬜ |
| Funnel (wide neck) | N/A | TILE REACTOR | ⬜ | ⬜ |
| Shovel | N/A | NaOH | ⬜ | ⬜ |
| Scoop | N/A | TILE IP.2 | ⬜ | ⬜ |
| Washing bottle | N/A | MeOH | ⬜ | ⬜ |
| Glass trays | N/A | TILE 1 | ⬜ | ⬜ |
| TILE 2 | ⬜ | ⬜ |
| TILE 3 | ⬜ | ⬜ |
| TILE 4 | ⬜ | ⬜ |
| TILE 5 | ⬜ | ⬜ |
| TILE 6 | ⬜ | ⬜ |
| TILE 7 | ⬜ | ⬜ |
| TILE 8 | ⬜ | ⬜ |
| **OTHER** | | | | |
| Working surfaces | N/A | N/A | ⬜ | ⬜ |
| Dry ice | 10 kg | N/A | N/A | N/A |
| 3 x Filtration cloth | cut for filter 046-5 | Sigma Aldrich, Z104256-5M | N/A | N/A |
| Tubing for peristaltic pump | N/A | TILE IP.2 solutions | ⬜ | ⬜ |
| Norprene hose | N/A | Tile solvent | ⬜ | ⬜ |
| PE waste bags | N/A | Solid waste, kategooria 3 | N/A | N/A |
| 8 x PE bag for trays | 360 x 560 mm | N/A | N/A | N/A |

| **TABLE 3.4 – PACKAGING AND SAMPLING MATERIALS CHECK-LIST** | | | |
| --- | --- | --- | --- |
| **Name** | **Size** | **Needed amount** | **Received amount** |
| **PACKAGING MATERIALS for product and samples** | | | |
| PE bags for packing final product | 550 x 700 mm | 4 |  |
| Closures | N/A | 8 |  |
| Amber glass vials with screw cap | 20 mL | 2 |  |
| **LABELS** | | | |
| For product | N/A | 2 |  |
| For samples | N/A | 2 |  |

| **PRODUCT LABEL reconciliation** (*filled by QA*) | | | |
| --- | --- | --- | --- |
|  | **Amount** | **Replacing/additional labels issued** | **QA signature** |
| Product labels returned to QA |  | ⬜ YES / ⬜ NO |  |

QA remarks:

**PROCEDURE**

| **No.** | **Description** | **Parameters** | | | | Operator’s signature  Verifier’s signature |
| --- | --- | --- | --- | --- | --- | --- |
| **Time** | | | **Other** |
| **1st working day \_ \_ . \_ \_ . \_ \_ \_ \_**  Temperature of room 257-2 has been registered in room logbook. | | | | | |  |
|  | NaOH solution for scrubber is prepared according to Table 1.1 and in the scrubber 053-1. Scrubber is connected to the reactor and checked (done by technical team). | \_\_:\_\_ | | |  |  |
|  | The reactor 002-17 and thermostat 011-22 are checked to be ready for work. Stirrer drive 021-30 is installed.  On lid (clockwise):   1. Reflux condenser on ball ground joint 2. 60 mm flange port (with lid) 3. Valve (loading of solvents). 4. Thermometer 003-209 5. Valve (unused in process, closed) 6. Overpressure release valve   Liquid dosage system – **disconnected**, not in use:   1. Dropping funnel 2. Rubber hose for filling (attached to filling valve of funnel) 3. PTFE tube – removed 4. Pressure balance tubing – removed   20 L receiver is **disconnected**, not in use:   1. Distillate receiving line – connected, valve on condenser – CLOSED; 2. Upper valve – is CLOSED; | The stirrer is in correct position and connected to the motor. Upon switching on the motor, the stirrer revolves in a stable manner: ⬜  The thermostat is connected and level of liquid is sufficient (recom­mended: medium level): ⬜  HTF piping is checked, no leaks are detected: ⬜  The reactor is visually clean: ⬜  Thermometer 003-209 is in the correct position: ⬜  Bottom valve of the reactor and closed: ⬜  Condenser is installed, tap water connected: ⬜  Reactor is grounded: ⬜  Checking is finished: \_\_:\_\_ | | | |  |
|  | **MeOH for reaction** is measured on balances 007-44 using tare function and charged into reactor using funnel ‘TILE TP.3 reactor’ though 60 mm flange port. Some MeOH (2 x 2.5 kg from required amount, into 2 jugs ‘Tile solvents’) is left for rinsing.  **Specified loading: 33.32 kg ( 33.12 - 33.52 kg)** | \_\_:\_\_ | | | Warehouse code:  ……………………  Charged mass:  . . . . . . . +. . . . . . . +  +. . . . . . . +. . . . . . . +  +. . . . . . . +. . . . . . . =  =……………. kg |  |
|  | Stirring is started. Suggested setting is 150‑180 RPM (recommended). | \_\_:\_\_ | | | Stirring setting:  …………….. RPM |  |
|  | **CuBr2** is weighed on balance 007-44 in portions into 5L jug ‘Tile reagents’. Material is charged into reactor using funnel ‘TILE TP.3 reactor’.  **Caution: material is heavy and corrosive!**  **Specified loading: 26.46 kg ( 26.06 - 26.86 kg)** | \_\_:\_\_ | | | Warehouse code:  ……………………  Charged mass:  . . . . . . . +. . . . . . . +  +. . . . . . . +. . . . . . . +  +. . . . . . . +. . . . . . . =  =……………. kg |  |
|  | Funnel ‘TILE TP.3 reactor’, jug ‘Tile reagent’ and walls of reactor are rinsed with **2.0 - 2.5 kg** of MeOH for reaction (from jug ‘TILE solvents’) to remove traces of CuBr2. | \_\_:\_\_ | | |  |  |
|  | **TILE IP.1 purified** is charged into reactor trough 60 mm flange port directly from it`s original tare using funnel ‘TILE TP.3 reactor’.  **Specified loading: 9.80 kg ( 9.75 - 9.85 kg)** | \_\_:\_\_ | | | Warehouse code:  ……………………  Gross weight  ………………………. kg  Weight of canister after discharging TILE IP.1 purified  ………………………. kg  Charged amount of TILE IP.1 purified, :  ………………………. kg |  |
|  | Funnel ‘TILE TP.3 reactor’ and walls are rinsed with **2.0 -** **2.5 kg** of MeOH for reaction (from jug ‘TILE solvents’). | \_\_:\_\_ | | |  |  |
|  | 60 mm flange port is closed with cover. | \_\_:\_\_ | | |  |  |
|  | Scrubber is started | \_\_:\_\_ | | | Scrubber is ON and functioning ⬜ |  |
|  | Thermostat 011-22 is switched on, temperature of the HTF is set to 70 oC. | \_\_:\_\_ | | | Temperature setting:  ………. oC |  |
|  | Heating of reaction mixture is started. Target: temperature of reaction mixture +60…+64⁰C (reading of thermometer 003-209) | Heating started:  \_\_:\_\_  Target achieved:  \_\_:\_\_ | | | Achieved temperature:  ……… oC |  |
|  | The goal is to achieve mild reflux of MeOH, while directing the vapours (HBr) into scrubber. There should be active bubbling in scrubber. | \_\_:\_\_ | | |  |  |
|  | Heating of reaction mixture is continued for 2.5…3.5 hours. Suggested stirring rate setting is 150-180 RPM. Temperature of reaction mixture should be in range **+60…+64⁰C.** Mild reflux of MeOH is expected.  Performance of reactor is recorded in Table 4 every 30-35 min.  Expected behaviour of reaction mixture: slowly turning from dark-green to more transparent green, formation of off-white precipitate (heavy, near the bottom). | Start  \_\_:\_\_  Finish  \_\_:\_\_ | | |  |  |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 4 - REACTION** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Thermostat setting, oC |  |  |  |  |  |  |  |  |  |  | | Reaction mixture temperature (003‑209 reading), oC |  |  |  |  |  |  |  |  |  |  | | Stirring rate of 021-30 |  |  |  |  |  |  |  |  |  |  | | Refluxing? (Y/N) |  |  |  |  |  |  |  |  |  |  | | | | | | | |
|  | After prescribed reaction time is out, the scrubber is stopped, and disconnected from reactor. pH of scrub solution is checked. If it is < 12, load solution from scrubber into barrel „Aqueous waste“ and discard. | \_\_:\_\_ | | | pH of solution: …………  If solution is discarded, mass of used scrubbing solution:  ..................... g |  |
|  | Thermostat 011-22 is set to **+15⁰C** (jacket temperature). Stirring of reaction mixture is continued; suggested setting is 150-180 RPM.  Cooling is continued until temperature of reaction mixture (003-209 reading) is in range +15...+25⁰C.  Performance of system is documented in Table 5 with 15-20 min intervals. | Cooling started:  \_\_:\_\_  Cooling finished:  \_\_:\_\_ | | |  |  |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 5 - COOLING OF THE REACTION MIXTURE** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | THERMOSTAT setting,  oC |  |  |  |  |  |  |  |  |  |  | | Reaction mixture temperature (reading of 003-209), oC |  |  |  |  |  |  |  |  |  |  | | Stirring rate, RPM |  |  |  |  |  |  |  |  |  |  | | | | | | | |
|  | Nutsche filter 046-5 is equipped with new cut of filtration cloth and connected to membrane pump 001-22 (setting 300-400 Torr). | | | \_\_:\_\_ | Pump:  ⬜ 001-22  ⬜ 001-… |  |
|  | Pump is started.  Reaction mixture is discharged trough the bottom valve out from reactor 002-17 portion-wise into 5 L jug ‘TILE TP.3’, transferred to Nutsche filter 046-5 and filtered.  **Attention!** Reaction mixture has corrosive properties. Avoid contact.  **Attention! Product has lachrymatory properties. Protect the eyes!** | | | Filtration is started:  \_\_:\_\_ |  |  |
|  | Walls and stirrer of reactor 002-17 are rinsed with **MeOH for rinsing the reactor from reaction mixture** with help of 1 L jug ‘MeOH’ and washing bottle ‘MeOH’.  **Specified loading: 3.60±0.2 kg**  Rinses are poured into filter 046-5 and used for rinsing the precipitate. Suction is continued. | | | \_\_:\_\_ | Amount of MeOH for rinsing the reactor:  …………. kg |  |
|  | Precipitate on filter is rinsed with additional amount of **MeOH for rinsing precipitate**.  **Specified loading:: 3.60±0.2 kg**  Suction is continued. | | | \_\_:\_\_ | Amount of MeOH for rinsing the reactor:  …………. kg |  |
|  | Reactor 002-17 is cleaned from the inside (walls, stirrer, bottom outlet valve):   1. rinsed with 1-2 L of acetone for cleaning; 2. rinsed with 3-5 L of 5 % aq. HCl for cleaning; 3. rinsing with 3-5 L of RO water 4. final rinsing with ~0.8 kg of MeOH for rinsing the reactor in the end of interim cleaning.   Cleanliness of reactor is assessed by visual inspection. Contact the production manager if there are difficulties with cleaning! | | | \_\_:\_\_ | Reactor is visually clean?  ⬜ Yes  Documented in 002-17 logbook?  ⬜ Yes |  |
|  | Pump 001-22 is stopped.  Appearance of inorganic precipitate on filter is documented. | | | Filtration is finished:  \_\_:\_\_ | Appearance of precipitate:  ........................... |  |
|  | Inorganic precipitate from filter is collected into double PE waste bag and weighed. Bag is labelled as ‘Solid waste, kategooria 3’ | | | \_\_:\_\_ | Weight of inorganic waste:  ....................... kg |  |
|  | Check that bottom outlet valve of reactor 002-17 is closed. | | | \_\_:\_\_ |  |  |
|  | **Attention! Product has lachrymatory properties. Protect the eyes!**  Filter 046-5 is opened. Filtrate containing the product IP.2 is pumped into reactor 002-17 using peristaltic pump 001-13 (or analogue) and tubing ‘TILE IP.2 solutions’.  Filtrate is transferred quantitatively.  It is possible that significant amount of needle-like crystals is present in the filtrate receiver.  IF present: the crystals are collected into 5L jug ‘TILE TP.3’, weighed and charged into reactor.  The product stays in reactor overnight. Stirring and thermostat are turned OFF. The reactor is closed. | | | \_\_:\_\_ | Amount of TILE IP.2 crystals:  ....................... kg |  |
|  | Total amount of MeOH used for reaction and washing is calculated (see Op. 3 + Op.19 + Op.20). | | | \_\_:\_\_ | Total amount of MeOH in solution:  ..................... kg |  |
|  | Apparatus of 1st day/ stage is cleaned. | | | \_\_:\_\_ |  |  |
| **2nd working day \_ \_ . \_ \_ . \_ \_ \_ \_**  Temperature of room 257-2 has been registered in room logbook. | | | | | |  |
|  | The reactor 002-17 and thermostat 011-22 are checked to be ready for work. Stirrer drive 021-30 is installed. System is prepared for evaporation of solvent under reduced pressure.  On lid (clockwise):   1. Reflux condenser on ball ground joint 2. 60 mm flange port (with lid) 3. Valve (loading of solvents). 4. Thermometer 003-209 5. Valve (unused in process, closed) 6. Overpressure release valve   Liquid dosage system – **disconnected**, not in use:   1. Dropping funnel 2. Rubber hose for filling (attached to filling valve of funnel) 3. PTFE tube – removed. 4. Pressure balance tubing –removed.   20 L receiver:   1. Distillate receiving line – connected, valve on condenser – OPEN; 2. Upper valve – no PTFE tube, connected to the top of the condenser via vacuum tubing and vacuum gauge; 3. ID 10 mm tubing connector is installed, connected to pump 001-22 **trough** cold trap. | The stirrer is in correct position and connected to the motor. Upon switching on the motor, the stirrer revolves in a stable manner: ⬜  The thermostat is connected and level of liquid is sufficient (recom­mended: medium level): ⬜  HTF piping is checked, no leaks are detected : ⬜  The reactor is visually clean: ⬜  Thermometer 003-209 is in the correct position: ⬜  Bottom valve of the reactor and closed: ⬜  Condenser is installed, tap water connected: ⬜  20 L receiver is assembled correctly: ⬜  Reactor is grounded: ⬜  Thermal insulation is in place: ⬜  Cold trap is connected: ⬜  Dry ice is available: ⬜  Checking is finished: \_\_:\_\_ | | | |  |
|  | Cooling water of the reactor condenser is opened. The jacket temperature is set to 70 °C. Stirring rate is set to 220…260 RPM (suggested, the mixing must be intensive to facilitate evaporation). | Heating started:  \_\_:\_\_  70⁰C in jacket (OUT) is reached:  \_\_:\_\_ | | | Cooling water is opened:  Yes: ⬜  011-22 temperature setting:  ……..… oC  Stirring setting:  ……… RPM |  |
|  | Vacuum pump 001-22 is turned on. Vacuum set starts with 300Torr and gradually reduced to 100Torr. | \_\_:\_\_ | | |  |  |
|  | Calculate amount of loaded methanol (Op.26). Calculate 85% and 90% of it.  **PM is responsible for verifying the calculations.** | \_\_:\_\_ | | | Total loaded MeOH:  ………….. kg  85% - ………kg  90% - ………kg | **PM signature** |
|  | The solution of IP.2 in methanol is concentrated until 85…90% of loaded methanol is recovered**.**  **Methanol to be collected: ..… - ..… kg (Op.31).**  **Recovered MeOH is collected (from receiver and cold trap) into canisters ‘Organic waste’ and discarded. Amount of waste is documented.**  Process parameters are registered in Table 6 with 25-30 min intervals.  NOTE: recommended pressure in the sys­tem is from 150 – 100Torr. Pump 001-22 is opera­ted at maximum flow rate but in a way to lessen the condensation in cold trap.  Recommended stirring rate: 220…260 RPM.  Expected mean evaporation rate is ~3.2…3.4 kg of MeOH/hour.  The receiver must be emptied as less frequently as possible, to avoid unnecessary interruption of the process. During the process empty the receiver when it is almost full. For that receiver is isolated from the reactor (all valves that connect receiver with reactor are closed). | Concentration started:  \_\_:\_\_  Concentration finished:  \_\_:\_\_ | | | Recovered MeOH:  1. ……………. kg  2. ……………. kg  3. ……………. kg  4. ……………. kg  5. ……………. kg  Total amount of MeOH:  …………………. kg  Operator`s notes:  …………………………..  …………………………. |  |
| |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **TABLE 6 - CONCENTRATION OF THE REACTION MIXTURE** | | | | | | | | Time (hh:mm) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  | | Receiving solvent? Y/N |  |  |  |  |  |  | | Vacuum reading, Torr |  |  |  |  |  |  | | Removed methanol, kg |  |  |  |  |  |  | | Total of removed methanol, kg |  |  |  |  |  |  | | **TABLE 6 - CONCENTRATION OF THE REACTION MIXTURE** | | | | | | | | Time (hh:mm) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  | | Receiving solvent? Y/N |  |  |  |  |  |  | | Vacuum reading, Torr |  |  |  |  |  |  | | Removed methanol, kg |  |  |  |  |  |  | | Total of removed methanol, kg |  |  |  |  |  |  | | **TABLE 6 - CONCENTRATION OF THE REACTION MIXTURE** | | | | | | | | Time (hh:mm) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  | | Receiving solvent? Y/N |  |  |  |  |  |  | | Vacuum reading, Torr |  |  |  |  |  |  | | Removed methanol, kg |  |  |  |  |  |  | | Total of removed methanol, kg |  |  |  |  |  |  | | | | | | | |
|  | Once prescribed amount of MeOH is removed vacuum is released and pump 001-22 (or analogue) is stopped. Stirring is continued.  Appearance of reaction mixture is documented. | \_\_\_:\_\_\_ | | | Appearance of the mixture after concentration:  …………………………  ……………………….. |  |
|  | Temperature of jacket is set to +40⁰C. Wait until jacket temperature is +40...+50⁰C (011-22 OUT reading). | Start  \_\_\_:\_\_  Finish  \_\_\_:\_\_\_ | | | Achieved jacket temperature:  ....................... ⁰C |  |
|  | **Water for production for extraction** is measured from canisters by weighting on balance 007-44 and charged into reactor 002-17 trough funnel ‘TILE TP.3 reactor’ while stirring (150…200 RPM – moderate the stirring to avoid splashing).  *Alternatively, the loading can be done by vacuum suction. Close the reactor, start the membrane pump (setting 300Torr), connect hose ‘Tile solvents’ to the valve ‘loading solvent’. Place the canister on the balance, tare the mass, insert the second end of the hose, and start suction by controlling the flow by bending the hose. Once required amount is loaded, take out the hose from the canister and let it be emptied into reactor. Stop the pump and continue with the process. The hose is dried by hanging vertically.*  **Specified loading: 32.34 kg ( 32.04 - 32.64 kg)** | \_\_\_:\_\_\_ | | | Warehouse code:  ………………………  Stirring set:  ................... RPM  Amount of water charged:  . . . . . . kg +. . . . kg +  +. . . .. kg + . .... .kg =  =................ kg |  |
|  | **n-heptane** **for 1st extraction** is measured in portions into 5 L plastic jug ‘Tile solvents’ on balances 007-44 and poured into reactor 002-17.  *Alternatively, the loading can be done by vacuum suction. Close the reactor, start the membrane pump (setting 450Torr), connect hose ‘Tile solvents’ to the valve ‘loading solvent’. Place the canister on the balance, tare the mass, insert the second end of the hose, and start suction by controlling the flow by bending the hose. Once required amount is loaded, take out the hose from the canister and let it be emptied into reactor. Stop the pump and continue with the process. The hose is dried by hanging vertically.*  **Specified loading: 26.46 kg ( 26.26 - 26.66 kg)** | \_\_\_:\_\_\_ | | | Warehouse code:  …………….  Amount of n-heptane charged:  . . . . . . kg +. . . . kg +  +. . . .. kg + . .... .kg =  =................ kg |  |
|  | The mixture in the reactor is stirred for 15…20 minutes at temperature +25….+40⁰C (mixture temperature).  Temperature of mixture (003-209) is registered in the beginning and in the end of stirring period. | Start of stirring:  \_\_:\_\_  End of stirring:  \_\_:\_\_ | | | Temperature of mixture:  In the beginning  .......................... ⁰C  In the end  .......................... ⁰C |  |
|  | Stirring is set to 10-15 RPM. Layers are allowed to separate for 8-12 min.  Expected appearance of mixture: bright green bottom layer (aqueous), brown upper layer (TILE IP.2 in n-heptane), off-white insoluble solid on the phase border. | Start of separation:  \_\_:\_\_  End of separation:  \_\_:\_\_ | | |  |  |
|  | Nutsche filter 046-5 is equipped with newly cut filtration cloth and is connected to membrane pump 001-22 (setting 300-400 Torr). | \_\_:\_\_ | | | Pump:  ⬜ 001-22  ⬜ 001-…. |  |
|  | Stirring is stopped completely. n-heptane layer containing the product is sucked out from reactor from the top using peristaltic pump 001-13 (or analogue) equipped with tubing ‘TILE IP.2 solutions’ and charged into filter 046-5. **Only clear n-heptane solution is taken**. In the end last litres of heptane layer are left in the reactor; do not take aqueous layer. | \_\_:\_\_ | | |  |  |
|  | Tubing ‘TILE IP.2 solutions’ is cleaned by rinsing with acetone for cleaning (inside and outside). | \_\_:\_\_ | | |  |  |
|  | **n-heptane for 2nd extraction** is measured in portions into 5 L plastic jug ‘Tile solvents’ on balances 007-44 and poured into reactor 002-17.  **Specified loading: 9.80 kg ( 9.60 - 10.00 kg)** | \_\_:\_\_ | | | Warehouse code:  …………….  Amount of n-heptane charged:  . . . . . . kg +. . . . kg +  +. . . .. kg + . .... .kg =  =................ kg |  |
|  | The mixture in the reactor is stirred for 10…15 minutes at temperature +25….+40⁰C (mixture temperature). Stirring rate: 180-220 RPM.  Temperature of mixture (003-209) is registered in the beginning and in the end of stirring period. | Start of stirring:  \_\_:\_\_  End of stirring:  \_\_:\_\_ | | | Stirring set: ......... RPM  Temperature of mixture:  In the beginning  .......................... ⁰C  In the end  .......................... ⁰C |  |
|  | Stirring is set to 10-15 RPM. Layers are allowed to separate for 8-12 min.  Expected appearance of mixture: bright green bottom layer (aqueous), light-brown upper layer (TILE IP.2 in n-heptane), off-white insoluble solid on the phase border. | Start of separation:  \_\_:\_\_  End of separation:  \_\_:\_\_ | | |  |  |
|  | Stirring is stopped completely. Aqueous layer and insoluble inorganic precipitate are discharged from the reactor 002-17 into canisters ‘Aqueous waste’.  Wastes are weighed and amounts are registered. | \_\_:\_\_ | | | Aqueous waste:   1. ..............kg 2. ..............kg 3. ..............kg 4. ..............kg 5. ..............kg 6. ..............kg   Total:  ..............kg |  |
|  | Thermostat 011-22 is switched off. | \_\_:\_\_ | | |  |  |
|  | Cooling water for condenser is switched off. | \_\_:\_\_ | | |  |  |
|  | n-heptane layer containing the product is discharged from the reactor 002-17 trough bottom valve portion-wise in to 5 L jug ‘TILE TP.3’ and charged in to filter 046-5. | \_\_:\_\_ | | |  |  |
|  | Filtration is finished once there is no liquid in the suspension receiver of the filter 046-5. | \_\_:\_\_ | | |  |  |
|  | Reactor 002-17 is cleaned from the inside (walls, stirrer, bottom outlet valve):   1. rinsed with 1-2 L of acetone for cleaning; 2. rinsed with 3-5 L of 5 % aq. HCl for cleaning; 3. rinsing with 3-5 L of RO water 4. final rinsing with ~0.5-1 L of acetone for cleaning 5. bottom outlet valve is closed   Cleanliness of reactor is assessed by visual inspection. Contact the production manager if there are difficulties with cleaning! | \_\_:\_\_ | | | Reactor is visually clean?  ⬜ Yes  Documented in 002-17 logbook?  ⬜ Yes |  |
|  | Filtrate containing the product is pumped into reactor 002-17 using pump 001-13 (or analogue) and tubing ‘TILE IP.2 solutions’. All of the filtrate is transferred.  It is possible that significant amount of colourless needle-like crystals is present in the filtrate receiver. IF present: the crystals are collected in to 5 L jug ‘TILE TP.3’, weighed and charged into reactor. | \_\_:\_\_ | | | Amount of crystals:  ....................... kg |  |
|  | Total amount of n-heptane used for extraction is calculated (see Op.36 + Op.42) | \_\_:\_\_ | | | Total amount of n-heptane in solution:  ..................... kg |  |
|  | Apparatus of 2nd day/ stage are cleaned | \_\_:\_\_ | | |  |  |
| **3rd working day \_ \_ . \_ \_ . \_ \_ \_ \_**  Temperature of room 257-2 has been registered in room logbook. | | | | | | |
|  | The reactor 002-17 and thermostat 011-22 are checked to be ready for work. Stirrer drive 021-30 is installed. System is prepared for evaporation of solvent under reduced pressure.  On lid (clockwise):   1. Reflux condenser on ball ground joint 2. 60 mm flange port (with lid) 3. Valve (loading of solvents). 4. Thermometer 003-209 5. Valve (unused in process, closed) 6. Overpressure release valve   Liquid dosage system – **disconnected**, not in use:   1. Dropping funnel 2. Rubber hose for filling (attached to filling valve of funnel) 3. PTFE tube - removed 4. Pressure balance tubing - removed   20 L receiver:   1. Distillate receiving line – connected, valve on condenser – OPEN; 2. Upper valve – no PTFE tube, connected to the top of the condenser via vacuum tubing and vacuum gauge; 3. ID 10 mm tubing connector is installed, connected to pump 001-22 **trough** cold trap. | The stirrer is in correct position and connected to the motor. Upon switching on the motor, the stirrer revolves in a stable manner: ⬜  The thermostat is connected and level of liquid is sufficient (recom­mended: medium level): ⬜  HTF piping is checked, no leaks are detected : ⬜  The reactor is visually clean: ⬜  Thermometer 003-209 is in the correct position: ⬜  Bottom valve of the reactor and closed: ⬜  Condenser is installed, tap water connected: ⬜  20 L receiver is assembled correctly: ⬜  Reactor is grounded: ⬜  Thermal insulation is in place: ⬜  Cold trap is connected: ⬜  Dry ice is available: ⬜  Checking is finished: \_\_:\_\_ | | | |  |
|  | Cooling water of the reactor condenser is opened. The jacket temperature is set to 70 °C.  Stirring rate is set to 220…260 RPM. | Heating started:  \_\_:\_\_  70⁰C in jacket (OUT) is reached:  \_\_:\_\_ | | | Cooling water is opened:  Yes: ⬜  011-22 temperature setting:  ……..… oC  Actual stirring speed:  ………. rpm |  |
|  | Vacuum pump 001-22 is turned on. Vacuum pump setting gradually reduced from 300 to 100Torr. | \_\_:\_\_ | | |  |  |
|  | The solution of IP.2 in n-heptane is concentrated until 85…90% of loaded heptane (see Op. 52) is recovered**.**  **PM is responsible to check the calculations before the process starts.**  **n-heptane to be collected: … - … kg.** | \_\_:\_\_ | | | Total loaded n-heptane:  ………….. kg  85% - ………kg  90% - ………kg | **PM sign.** |
|  | **Recovered n-heptane is collected (from receiver and cold trap) into canisters ‘Organic waste’ and discarded. Amount of waste is documented.**  Process parameters are registered in Table 7 with 25-30 min intervals.  NOTE: recommended pressure in the system is 300-100Torr. Pump 001-22 is operated at maximum flow rate but in a way to lessen the condensation in cold trap.  Recommended stirring rate: 220…260 RPM.  Expected mean evaporation rate is ~6.2…6.4 kg of n-heptane/hour  The receiver must be emptied as less frequently as possible, to avoid unnecessary interruption of the process. During the process empty the receiver when it is almost full. For that receiver is isolated from the reactor (all valves that connect receiver with reactor are closed). | Concentration started:  \_\_:\_\_  Concentration finished:  \_\_:\_\_ | | | Recovered n-heptane:  1. …………………. kg  2. …………………. kg  3. …………………. kg  4. …………………. kg  5. …………………. kg  Total amount of  n-heptane:  ………………………. kg  Operator`s notes:  ………………………..  ………………………… |  |
| |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **TABLE 7 - CONCENTRATION OF THE IP.2 SOLUTION** | | | | | | | | Time (hh:mm) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  | | Receiving solvent? Y/N |  |  |  |  |  |  | | Vacuum reading, Torr |  |  |  |  |  |  | | Removed n-heptane, kg |  |  |  |  |  |  | | Total volume of removed n-heptane, kg |  |  |  |  |  |  | | **TABLE 7 - CONCENTRATION OF THE IP.2 SOLUTION** | | | | | | | | Time (hh:mm) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  | | Receiving solvent? Y/N |  |  |  |  |  |  | | Vacuum reading, Torr |  |  |  |  |  |  | | Removed n-heptane, kg |  |  |  |  |  |  | | Total volume of removed n-heptane, kg |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **TABLE 7 - CONCENTRATION OF THE IP.2 SOLUTION** | | | | | | | | Time (hh:mm) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  | | Receiving solvent? Y/N |  |  |  |  |  |  | | Vacuum reading, Torr |  |  |  |  |  |  | | Removed n-heptane, kg |  |  |  |  |  |  | | Total volume of removed n-heptane, kg |  |  |  |  |  |  | | | | | | | |
|  | Once prescribed amount of n-heptane is removed, pump 001-22 is stopped. Stirring is continued. Pressure is increased to 300-400Torr and kept for next loading.  Appearance of reaction mixture is documented. | \_\_\_:\_\_\_ | | | Appearance of the mixture after concentration:  …………………….. |  |
|  | **Anhydrous ethanol for recrystallization** is measured from canisters by weighting on balance 007-44 and sucked into reactor 002-17 using vacuum, while stirring (150…200 RPM).  *For that, connect hose ‘Tile solvents’ to the valve ‘loading solvent’. Place the canister with solvent on the balance, tare the mass, insert the second end of the hose, and start suction by controlling the flow by bending the hose. Once required amount is loaded, take out the hose from the canister and let it be emptied into reactor. Continue with the process. The hose is dried by hanging vertically.*  **Specified loading: 7.74 kg ( 7.64 - 7.84 kg)** | \_\_\_:\_\_\_ | | | Warehouse code:  …………….  Stirring set:  ................... RPM  Amount of EtOH charged:  . . . . . . kg +. . . . kg +  +. . . .. kg + . .... .kg =  =................ kg |  |
|  | Temperature of jacket is set to +80⁰C. Wait until jacket temperature is +70...+80⁰C (011-22 OUT reading). | Start:  \_\_\_:\_\_\_  Finish:  \_\_\_:\_\_\_ | | | Achieved jacket temperature:  ....................... ⁰C |  |
|  | Mixture is heated up to temperature +50...+75⁰C while stirring (150…200 RPM). The goal is to achieve **clear and uniform solution.**  Temperature of reaction mixture in the end of operation mixture is documented.  Note: TILE IP.2 product has low melting point and in liquid state mixes well with ethanol, so it is not necessary to wait until ethanol reflux begins. | Start:  \_\_\_:\_\_\_  Finish:  \_\_\_:\_\_\_ | | | Achieved mixture temperature (003‑209):  ....................... ⁰C |  |
|  | Once TILE IP.2 is dissolved, cooling is started. Thermostat 011-22 is set to +25⁰C. Wait until jacket temperature is +25...+30⁰C (011-22 OUT reading). | Start:  \_\_\_:\_\_\_  Finish:  \_\_\_:\_\_\_ | | | Achieved jacket temperature:  ....................... ⁰C |  |
|  | Condenser cooling water is switched off. | \_\_\_:\_\_\_ | | |  |  |
|  | Crystallization of TILE IP.2 is continued. The goal is **to reach -22...-18⁰C** in reaction mixture **and stir** the mixture at this temperature **for** **2…2.5 hours** (after passing checkpoint 3).  Performance of the system is documented in Table 8 every 15-20 min.  Recommended stirring rate is 200-250 RPM.  **NB! At all times maximum allowed difference between temperature of mixture and reactor walls is 55⁰C.**  Checkpoints:   * + - 1. Wait until temperature of reaction mixture is in range +30...+35⁰C and set jacket temperature to -25⁰C.  1. Wait until temperature of jacket is ‑25…‑20⁰C. 2. Wait until temperature of crystallization mixture is -22...-18⁰C and set jacket temperature to -22⁰C | Start:  \_\_\_:\_\_\_  Check-point  1: \_\_\_:\_\_\_  Check-point  2: \_\_\_:\_\_\_  Check-point  3: \_\_\_:\_\_\_  Finish:  \_\_\_:\_\_\_ | | | Time when temperature of HTF reached  -25…-20⁰C:  \_\_\_:\_\_\_ |  |
| |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 8 - CRYSTALLIZATION OF TILE IP.2** | | | | | | | | | | Time (HH:MM) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  |  |  | | Precipitate present? Y/N |  |  |  |  |  |  |  |  | | **TABLE 8 - CRYSTALLIZATION OF TILE IP.2** | | | | | | | | | | Time (HH:MM) | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | \_\_\_:\_\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  | | Stirring rate 021-30, RPM |  |  |  |  |  |  |  |  | | Precipitate present? Y/N |  |  |  |  |  |  |  |  | | | | | | | |
|  | Nutsche filter 046-5 is equipped with newly cut filtration cloth and is connected to membrane pump 001-22 (setting 300‑400Torr). | \_\_:\_\_ | | | Pump:  ⬜ 001-22  ⬜ 001-… |  |
|  | Pump is started.  Crystallization mixture is discharged from the reactor 002-17 trough bottom valve portion-wise in to 5 L jug ‘TILE TP.3’ and charged on the filter 046-5.  Suction is stopped once there is no visible liquid in suspension receiver.  **Attention! Product has lachrymatory properties. Protect the eyes** | Start of filtration:  \_\_:\_\_  End of filtration:  \_\_:\_\_ | | |  |  |
|  | The drying oven 012-13 is set to a temperature 25°C. The fаn is set to 80% (Setting 8), flap is opened to maximum.  **NB! It is important to start the oven at least a couple of hours before product is inserted to give it enough time to stabilize the temperature.** | \_\_\_\_:\_\_\_\_ | | | Temperature setting:  ……….… °C  The fan setting:  ………… % |  |
|  | **Anhydrous ethanol for rinsing the reactor and precipitate** is weighed in original tare on balances 007-44 and charged into reactor 002‑17 in a way to rinse the walls properly.  **Specified loading: 11.76 kg ( 11.66 - 11.86 kg)** | \_\_:\_\_ | | | Amount of EtOH for rinsing:  . . . . . kg +. . . . kg +  +. . . .. kg + . .... .kg =  =................ kg |  |
|  | Anhydrous ethanol for rinsing is discharged from reactor 002-17 portion-wise in to 5 L jug ‘TILE TP.3’ and charged into filter 046-5. Precipitate is mixed thoroughly on filter. | \_\_:\_\_ | | |  |  |
|  | Suction is resumed and continued for 20‑30 min. Filter cake is pressed using plastic scoop ‘TILE IP.2’ and/or using big spatula.  **Attention! Product has lachrymatory properties. Protect the eyes. Keep the filter closed with lid whenever possible.** | Start of filtration:  \_\_:\_\_  End of filtration:  \_\_:\_\_ | | |  |  |
|  | Glass trays ‘TILE 1 ...8’(with a PE bag on the bottom) weighed on balances 007-44. Table 9 is filled. | \_\_:\_\_ | | |  |  |
|  | Product is loaded onto trays in an efficient manner. Layer thickness is limited with height of tray walls. Appearance of the product is documented. | \_\_:\_\_ | | | Appearance of the product:  ………………………… |  |
|  | Trays with product are weighed on balances 007-44, results are registered in Table 9. Total mass of wet product is calculated. | \_\_\_\_:\_\_\_\_ | | |  |  |
|  | The filtrate from the Nutsche filter is drained into the canister **‘Crystallization mother liquor’**, weighed, recorded in the Batch Record and **KEPT SEPARATELY as EXPERIMENTAL WASTE.** | \_\_\_\_:\_\_\_\_ | | | Crystallization mother liquor:  **(marked as EXPERIMENTAL WASTE):**  ……………. kg |  |
|  | The trays ‘TILE 1’ … ‘TILE 8’ with wet product are inserted into the drying oven 012‑13. | \_\_\_\_:\_\_\_\_ | | |  |  |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 9 - Drying of product** | | | | | | | | | | | |  | | TILE 1 | TILE 2 | TILE 3 | TILE 4 | TILE 5 | TILE 6 | TILE 7 | TILE 8 | **Total** | | **Before** drying | Tare weight of tray+ PE bag, g |  |  |  |  |  |  |  |  |  | | Weight of tray with wet pro­duct before drying, g |  |  |  |  |  |  |  |  |  | | Calculated weight of the wet product, g |  |  |  |  |  |  |  |  |  | | **After** drying | Weight of tray with product after drying, g |  |  |  |  |  |  |  |  |  | | Calculated weight of the dried product, g |  |  |  |  |  |  |  |  |  | | | | | | | |
|  | Check that the temperature in the oven is in range 25-30°C. Insert the trays with the product into the oven. Otherwise wait until temperature is in range. | \_\_\_\_:\_\_\_\_ | | | Temperature of the oven:  …….. °C |  |
|  | The product is dried in oven 012-13 at 25°C for 16-24 hours (total time).  After the initial 12-15 hours of drying, the product is mixed on trays. Drying is continued for at least 3 hours after mixing. | Drying started at:  \_\_ /\_\_  dd/mm,  \_\_\_\_:\_\_\_\_  hh:mm  Mixing:  \_\_ /\_\_  dd/mm,  \_\_\_\_:\_\_\_\_  hh:mm  Drying finished at  \_\_ /\_\_  dd/mm,  \_\_\_\_:\_\_\_\_  hh:mm  Total time:  \_\_\_\_:\_\_\_\_  hh:mm | | | Temperature in 012-13 when mixing  ….…°C  Temperature at the end:  …..…… °C |  |
|  | Apparatus of 3rd working day/stage is cleaned | \_\_\_\_:\_\_\_\_ | | |  |  |
| **4th working day \_ \_ . \_ \_ . \_ \_ \_ \_**  Temperature of room 257-2 has been registered in room logbook. | | | | | |  |
|  | At the end of drying period drying oven 012-13 is switched OFF | | \_\_:\_\_ | | Time is recorded in Op 77: ⬜ |  |
|  | The glass trays with dried product are weighed on balance 007-44. The weights are recorded in Table 9. | | \_\_:\_\_ | | Data is recorded in Table 9: ⬜ |  |
|  | Samples for analysis and retention are taken from the product according to sampling procedure.  Sampling protocol (QD-LC) and Table 10 – Part 1 are filled. Photocopies of labels are taken. | | \_\_:\_\_ | | Sampling protocol is filled: ⬜  Photocopies of sample labels are taken:  ⬜ |  |
|  | Primary package of the product (PE-bag) is labelled. The product is packaged into PE bag, closed with 2 closures and labelled. Then the primary package with the product is inserted into second PE-bag and the second package is closed with 2 closures.  Table 10 – Part 2 is filled.  Photocopies of labels are taken. | | \_\_:\_\_ | | Table 10-Part 2 is filled: ⬜  Photocopies of product labels are taken:  ⬜ |  |
|  | Yield of process is calculated:  – see Table 9-Part 2.  – see Op.7. | | \_\_:\_\_ | | Calculated amount:  ………. kg  Yield:  ....................% |  |
|  | All used apparatus is clean (see Table 3). | | \_\_:\_\_ | |  |  |

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| **TABLE 10** | | | | | | | | |
| **Part 1 - PACKING of the SAMPLES** | | | | | | | | |
| **Type of packaging**  **(required amount)** | **Tare weight [g]** | | **Gross weight (container+**  **sample) [g]** | **Net weight of the sample [g]** | **Package is correctly closed** | | **Label is correct and added** | **Operator’s signature**  **Verifier’s**  **signature** |
| **Vial 1: for analysis**  **(NLT 1 g)** |  | |  |  | ⬜ | | ⬜ |  |
| **Vial 2: for retention**  **(NLT 2 g)** |  | |  |  | ⬜ | | ⬜ |
| **Sum of packaged samples [g]** | | | |  | **Production manager’s**  **Signature:** | | | |
| **Part 2 - PACKING of the PRODUCT** | | | | | | | | |
| **Type of packaging**  **(required amount)** | **Tare weight [kg]** | **Gross weight (container+**  **product) [kg]** | | **Net weight of the product [kg]** | **Package is correctly closed** | **Label is correct and added** | | **Operator’s signature**  **Verifier’s**  **signature** |
| **PE-bag 1: Product** | PE-bag + 2 closures + label: |  | |  | ⬜ | ⬜ | |  |
| **PE- bag 2: Product** | PE-bag + 2 closures + label: |  | |  | ⬜ | ⬜ | |  |
| **Sum of packaged product [kg]** | | | |  | **Production manager’s**  **Signature:** | | | |

**GIVING OVER THE PRODUCT AND SAMPLES:**

| **Description** | **Time** | **Signatures** |
| --- | --- | --- |
| The retention sample and the product are given to warehouse (room 259).  Product is wrapped into a **dark PE bag** to protect it from light.  **This date and time are added by Production Manager as "Process finished at” on the first page.** | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ | **Operator**  **Warehouse** |
| The analysis sample is given to QC laboratory for analysis. | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ | **Operator** |

**CHECKS AND CONFIRMATIONS BY PRODUCTION MANAGER:**

| **Description** | **Time** | **PM’s signature** |
| --- | --- | --- |
| All equipment, utilities used in the process are cleaned and stored. Cleaning check-list is filled, Table 3. (**PM is responsible for performing on-site check.)** | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ |  |
| Photograph(s) of product in double PE-bag have been checked by PM confirming that the product is packaged correctly. | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ |  |
| Photocopies of labels are added to respective fields in Table 11 **(PM is responsible).** | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ |  |
| Thermostat log is reviewed. | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ |  |

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| **TABLE 11 – EXAMPLES OF THE LABELS** */Ask QA for label templates/* | |
| For **SAMPLES** | |
| Template of the label:   |  | | --- | | **(1-Bromocyclopentyl)-2-thienyl ketone**  **(TILE IP.2)**  **ANALYSIS**  Batch No: TBD-0322-X IP.2  **Date:** ..............................................  **Sample amount:** ............................  **Operator’s signature:** ....................  **Storage conditions:** dark, below 30 °C | | **(1-Bromocyclopentyl)-2-thienyl ketone**  **(TILE IP.2)**  **RETENTION**  Batch No: TBD-0322-X IP.2  **Date:** ..............................................  **Sample amount:** ............................  **Operator’s signature:** ....................  **Storage conditions:** dark, below 30 °C | | Used label (photo-copy): |

|  |  |
| --- | --- |
| For **PRODUCT** | |
| Template of the label: | Used label (photo-copy): |
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| **TABLE 12 – OBTAINED MATERIALS** | | | | |
| **Product** | | | | |
| **Name** | **Calculated amount [kg]** | **Actual amount**  **[kg]** | **Calculated yield**  **[%]** | **Signatures** |
| (1-Bromocyclopentyl)-2-thienyl ketone | See Op.84 | See Table 10 – Part 2 | See Op. 84  Expected: 70-78% | **PM** |
| **Waste** */waste category is assigned according to juhend „Keemiliste jääkide kogumine ja käitlemine“ (Lisa.1)/* | | | | |
| **Name** | **Category** | **Actual amount**  **[kg]** | **Destination** | **Signatures** |
| Waste - insoluble inorganic salts  Op.23 | 3 |  | Discarded | **Operator**  **PM** |
| Waste - MeOH  Op.32 | 1 |  | Discarded |
| Waste – aqueous  Op.45 | 2 |  | Discarded |
| Waste - heptane  Op.58 | 1 |  | Discarded |
| Waste - mother liquor  Op.75 | 1 |  | **Kept for at least 1 month.** |
| **Material loss** |  |  |  |
| **TOTAL AMOUNT:** | |  |  |

Material loss = total amount - all waste - product (Table 10 – Part 2)

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| **Deviations during batch production** | |
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| **Production Manager (date, signature):** | **\_ \_ . \_ \_ . \_ \_ \_ \_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** |
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| **Deviations reviewed by QA, comments:** | |
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| **QA (date, signature):** | **\_ \_ . \_ \_ . \_ \_ \_ \_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** |

**FINISHING THE BATCH RECORD:**

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| --- | --- | --- | --- |
| **Quality Assurance** | | **Date** | **Signature** |
| ⬜ | **Batch Record is reviewed** |  |  |
| ⬜ | **Analysis results and CoA are reviewed** |  |  |
| ⬜ | **CoA is attached to the batch record** |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Production Manager** | | **Date** | **Signature** |
| ⬜ | **Batch Record is reviewed** |  |  |
| **The results of analysis correspond to quality specification.** | |  |  |
| ⬜ | **YES** |
| ⬜ | **NO**  ⬜ Directed to reprocessing.  ⬜ Other:  ………………………………………. |

**Batch record is COMPLETed and Presented data is ACCURATE.**

|  |  |  |
| --- | --- | --- |
| **Signed by** | **Date** | **Signature** |
| **Production Manager:** |  |  |
| **Quality Assurance:** |  |  |

**References (if necessary; BRP code in case of final product):**