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

|  |  |
| --- | --- |
| **REFERENCES:** | |
| Manufacturing SOP: | MD-SOP TILE (current version) |
| Validation Report: | 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]** |
| **Cyclopentanecarboxylic acid (CPCA, TILE SM2)**  (Op. 7)  **(Starting material of this TP)** | (Example: TILE SM2 XXX) | Assay NLT 93.0% | 1 kg | **Min-max loading 6.0-17.5 kg**  ..… kg  ( ..… - ..… kg) |  |
| **Polyphosphoric acid (PPA)**  (Op. 9)  NB! At least 10% excess of polyphosphoric acid is taken for warming up. Excess of polyphosphoric acid is returned to the warehouse. | (Example: PPA XXX) | Assay 83.0…87.0 % as P2O5 | 0.98 ± 0.05 kg | ..… kg  ( ..… - ..… kg) |  |
| **Thiophene (TILE SM1)**  (Op. 11) | (Example: THIOPHENE XXX) | Assay NLT 99.0%  ρ=1.05 g/mL | 0.80 ± 0.02 kg | ..… kg  ( ..… - ..… kg) |  |
| **Water for production (Water PR)**  **Water for production (Water PR)** | (Example:  013-XX dd/mm/yy HH:MM) | conductivity NMT 4.3 µS\*cm-1  Use within 2 days after collection  b.p. 100⁰C | For quenching | | |
| 1.20 ± 0.10 kg | ..… kg  ( ..… - ..… kg) |  |
| For ~42% KOH solution preparation | | |
| 0.21 ± 0.10 kg | ..… kg  (..… - ..… kg) |  |
| For sodium chloride (NaCl) saturated solution preparation | | |
| ~1.20 kg | ..… kg  (..… - ..… kg) |  |
| **Water for production total: ~2.7 kg per 1 kg of starting material** | | |
| **~42% KOH solution**  (Op. 17)  (See Table 1.2 for preparation) |  | ~42 w/w % KOH  ρ=1.51 g/mL | 0.42 kg ± 0.02 kg | ..… kg  ( ..… - ..… kg) |  |
| **Sodium chloride (NaCl) saturated solution**  (See Table 1.3 for preparation) |  | Saturated solution  ρ=1.2 g/mL | For dilution | | |
| 0.49 ± 0.02 kg | ..… kg  ( ..… - ..… kg) |  |
| For rinsing | | |
| 0.73± 0.04 g | ..… kg  ( ..… - ..… 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: |

\* Materials (e.g. solutions) are prepared in small excess. Only the amount actually used in process is written into the Table 1. Any unused materials and amounts of them are written into **TABLE 9.2** Unused materials and solutions.

| **TABLE 1.2– PREPARATION OF ~42% KOH SOLUTION** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| 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-\_\_\_\_\_\_\_\_\_\_\_\_\_ \_ \_ . \_ \_ . \_ \_ \_ \_**  ⬜ **Preparation:** Water for production is measured into 25 L canister ‘conc. KOH solution’ by weighting on balances 007-42. The canister is placed into plastic bath; bath is then filled with ice (10-20 kg). Potassium hydroxide is weighted in ca 1 kg portions into 1 L plastic jug ‘KOH’ and charged into canister using funnel ‘AQ. SOLUTIONS’, canister is shaken after addition of each portion.  The solution heats up during dissolution!  Dissolution of KOH is controlled visually. | | | | | |  |
| **Potassium hydroxide (KOH)** | (Example: KOH XXX) | Assay NLT 85.0% of KOH | 0.21 ± 0.10 kg | ..… kg  (..… - ..… kg) |  |  |
| **Water for production (Water PR)** | (Example:  013-XX dd/mm/yy HH:MM) | conductivity NMT 4.3 µS\*cm-1  Use within 2 days after collection  b.p. 100⁰C | 0.21 ± 0.10 kg | ..… kg  (..… - ..… kg) |  |  |
| **Preparation date, time:** | | | | **\_ \_ . \_ \_ . \_ \_ \_ \_** \_\_\_\_ : \_\_\_\_ | |  |

| **TABLE 1.3– PREPARATION OF SODIUM CHLORIDE (NaCl) SATURATED SOLUTION** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| 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-\_\_\_\_\_\_\_\_\_\_\_\_\_ \_ \_ . \_ \_ . \_ \_ \_ \_**  ⬜ **Preparation:** 25 L plastic canister ‘Sat. Aq. NaCl’ is equipped with funnel ‘AQ. SOLUTIONS’. Canister with funnel is put on the balance, which is tared. NaCl is weighed into 25 L plastic canister ’ Sat. Aq. NaCl’ on balance 007-42 using funnel ’AQ. SOLUTIONS’, balance is tared again. Water for production for preparation of saturated NaCl solution is then measured by weight into the canister using the same funnel and balances. The solution in the canister is mixed by shaking for at least 3 x ~1 min with 10…30 min intervals. The presence of precipitate in the solution is confirmed by visual check. If necessary, additional amount of NaCl is added. Addition is recorded. | | | | | |  |
| **Sodium chloride (NaCl)** | (Example: MARO NaCl XXX) | Assay (dried substance)  99.0 – 100.5 % | ~0.48 kg | ..… kg  (..… - ..… kg) |  |  |
| **Water for production (Water PR)** | (Example:  013-XX dd/mm/yy HH:MM) | conductivity NMT 4.3 µS\*cm-1  Use within 2 days after collection  b.p. 100⁰C | ~1.20 kg | ..… kg  (..… - ..… kg) |  |  |
| **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  ⬜ respirators (protection from organics vapors e.g. with brown stipes cartridge) |  |
| Fire protection equipment is present. |  |
| Calibration solutions for pH-meter are available and valid.   |  |  | | --- | --- | | **Solution** | **Valid until**  (DD/MM/YYYY) | | pH 7.0 | \_ \_ . \_ \_ . \_ \_ \_ \_ | | pH 10.0 | \_ \_ . \_ \_ . \_ \_ \_ \_ | |  |
| Ice for water bath cooling is available (min 20 kg). |  |
| Solvents and solutions for equipment and glassware cleaning are present:  ⬜ Acetone for cleaning  ⬜ DCM  ⬜ RO water, e.g. from 013-16 |  |

| **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 with   * Stirrer (pitched blade turbine) * stirrer drive 021-20 * reflux condenser * overpressure release valve * liquid addition system with dip pipe pointed to center. * 20L receiver | 002-17 | ⬜ | ⬜ | ⬜ | **Yes** ⬜ **No** ⬜ |
| Heating/cooling circulator, HTF – Syltherm XLT | 011-22 | ⬜ | ⬜ | N/A | N/A |
| Ca 80 L plastic bath | N/A | ⬜ | ⬜ | N/A | N/A |
| Membrane pump with controller | ⬜ 001-47 oranalogue  ⬜ 001- … | ⬜ | ⬜ | N/A | N/A |
| Drying oven | 012-13 | ⬜ | ⬜ | ⬜ | **Yes** ⬜ **No** ⬜ |
| **OTHER EQUIPMENT** | | | | | |
| pH meter | ⬜ 005-8 or analogue  ⬜ 005- … | ⬜ | ⬜ | ⬜ | N/A |
| ClearLine® pH paper (strips), pH 0 - 14 |  | ⬜ |  |  |  |

| **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 60 kg) | 007-42 | ±1 g | **\_ \_ . \_ \_ \_ \_**  Metrosert | ⬜ | ⬜ |
| Balance (max 2.0 kg) | 007-10 | ±0.01 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 | 25L | Sat. Aq. NaCl | ⬜ | ⬜ |
| Canister | 25L | conc. KOH solution | ⬜ | ⬜ |
| Canister | 25L | AQUEOUS WASTE  ACIDIC WASTE, DO NOT MIX WITH OTHER WASTE | ⬜ | ⬜ |
| Canister | 25L | AQUEOUS WASTE  BASIC WASTE, DO NOT MIX WITH OTHER WASTE | ⬜ | ⬜ |
| Canister | 25L | AQUEOUS WASTE | ⬜ | ⬜ |
| **UTENSILS** | | | | |
| Jug | 3 x 5L | TILE | ⬜ | ⬜ |
| Jug | 3L | CPCA | ⬜ | ⬜ |
| Jug | 3L | THIOPHENE | ⬜ | ⬜ |
| Jug | 1L | TILE | ⬜ | ⬜ |
| Jug | N/A | Cleaning | ⬜ | ⬜ |
| Funnel | N/A | AQ. SOLUTIONS | ⬜ | ⬜ |
| Funnel | N/A | TILE IP.1, crude | ⬜ | ⬜ |
| Funnel (wide neck) | N/A | TILE reactor | ⬜ | ⬜ |
| Shovel | N/A | KOH | ⬜ | ⬜ |
| Spoons and spatulas (x4) | N/A | N/A | ⬜ | ⬜ |
| **OTHER** | | | | |
| Working surfaces | N/A | N/A | ⬜ | ⬜ |
| Flashlight (for checking separation of layers) | N/A | N/A | N/A | N/A |
| **DISPOSABLES** | | | | |
| Indicator paper | N/A | (ChemLand, pH 1-14, 000501.001) | ⬜ | N/A |

| **TABLE 3.4 – PACKAGING AND SAMPLING MATERIALS CHECK-LIST** | | | |
| --- | --- | --- | --- |
| **Name** | **Size** | **Needed amount** | **Received amount** |
| **PACKAGING MATERIALS for product and samples** | | | |
| Canister | 10L | 2 |  |
| 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. | | | |  |
|  | The drying oven 012-13 is set to temperature 60 oC.  **Verify that there is no timer activated.** | \_\_:\_\_ | Setting:  ………… oC |  |
|  | **Polyphosphoric acid (PPA),** at least 10% more than required quantity (see Table 1), is placed into drying oven in original bottles.  **Specified loading: ..... kg ( ..... – ..... kg)**  PPA is warmed in drying oven for at least 12 h, until it is used in Op. 9. | Melting is started at:  \_\_:\_\_ | Warehouse code:  …………………….  Weight of material put into drying oven:  . . . . . . . . . . . kg |  |
|  | Apparatus/working surface of 1st day/stage is cleaned. | \_\_:\_\_ |  |  |

| **No.** | **Description** | **Parameters** | | Operator’s signature  Veri­fier’s signature |
| --- | --- | --- | --- | --- |
| **Time** | **Other** |
| **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 021-20 is installed.  On lid (clockwise):   1. Reflux condenser on ball ground joint 2. 60 mm flange port (with lid) 3. Liquid dosage port (connected to dropping funnel) 4. Thermometer 003-209 5. Valve (unused in process, closed) 6. Overpressure release valve   Liquid dosage system:   1. Dropping funnel with dip pipe to direct of addition into center of reactor. 2. Rubber hose for filling (attached to filling valve of funnel) 3. PTFE tube (connected to 3. on lid) 4. Pressure balance tubing (connected to 3. on lid via one-way valve; connected to pump 001-47 via T-adapter)   20 L receiver is not connected to the rest of the system, not used in process. | 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: ⬜  Thermosensor 003-209 is in the correct position: ⬜  Bottom valve of the reactor and closed: ⬜  Condenser is installed, tap water connected: ⬜  Liquid dosage system is assembled correctly: ⬜  Reactor is grounded: ⬜  Checking is finished: \_\_:\_\_ | |  |
|  | Thermostat 011-22 is switched on, temperature of the HTF is set to 60 oC. | \_\_:\_\_ | temperature setting:  …. oC  manometer on thermostat 011-22:  ......... MPa  manometer on reactor 002-17:  ......... MPa |  |
|  | Wait until temperature of HTF reaches 50...60 oC **(RETURN temperature)** | Reached at  \_\_:\_\_ | Reached RETURN temperature:  …………….. oC |  |
|  | Starting material **Cyclopentanecarboxylic acid** (CPCA) is weighed in original tara using the balance 007-42, then pumped into reactor using peristaltic pump and hose “reagents”.  **NB! Opening and handling of CPCA should be done under the hood with good ventilation.**  **Specified loading: ..... kg ( ..... – ..... kg)** | \_\_:\_\_ | Warehouse code:  …………….  Actual loading:  .......... + ...............+  +..............+.............+  +..............+.............+  **=......................... kg** |  |
|  | Stirrer of reactor 002-17 is activated, recommended stirring rate is set to 150-180 RPM. Intensive agitation is required (by visual observation).  **NB! Intensive stirring during mixing of PPA and CPCA is important.** | \_\_:\_\_ | Stirring setting  ….............. rpm |  |
|  | Required amount of **PPA** is charged into reactor 002-17 using funnel „TILE reactor“. Original bottles of pre-heated PPA are placed on balances 007-42, tared and emptied into reactor, then placed back on balance. Weights are recorded.  **Specified loading: ..... kg ( ..... – ..... kg)**  Expected behaviour of reaction mixture:   * Slow intermixing of PPA and CPCA, without noticeable temperature effect; * appearance of brown colour; increase of viscosity of reaction mixture. * If the temperature drops during addition, keep heating and addition, no need to pause. | Started  \_\_:\_\_  Finished  \_\_:\_\_ | Temperature in 012-13:  .................. oC  **loaded PPA amounts**  Bottle 1: …......... kg  Bottle 2: …......... kg  Bottle 3: …......... kg  Bottle 4: …......... kg  Bottle 5: …......... kg  Bottle 6: …......... kg  Bottle 7: …......... kg  Bottle 8: …......... kg  **SUM: .............….. kg** |  |
|  | Liquid dosage system: close valve on pressure equalizing line, set pump 001-47 to 400...500 Torr vacuum and create underpressure in dropping funnel. | \_\_:\_\_ |  |  |
|  | Starting material **Thiophene** (portion 1, see Table 4 below) is measured into jug „THIOPHENE“ using balances 007-42. Measured amount is charged into dropping funnel of the reactor using vacuum. After charging is complete vacuum is released and pump is stopped.  **NB! Opening and handling of Thiophene is done under the hood with good ventilation.**  Stirring setting 200-240rpm.  **Specified loading: ..... kg ( ..... – ..... kg)**  25% - ......................... kg  25% - ......................... kg  25% - ......................... kg  25% - ......................... kg | \_\_:\_\_ | Warehouse code:  …………….  Measured amount:  portion 1 (25%):  ................... kg  portion 2 (25%):  ................... kg  portion 3 (25 %):  ................... kg  portion 4 (25%):  ................... kg  **TOTAL measured amount:**  **................... kg** |  |
|  | Thermostat is set to jacket temperature 30⁰C. | \_\_:\_\_ | Temperature setting:  ..................…. oC |  |
|  | Open tap water valve that is connected to condenser. | \_\_:\_\_ |  |  |
|  | Stirring of reaction mixture is increased to 200...250 RPM.  Pay attention to vibration of the system; set slower stirring rate if vibration is too intensive and contact the production manager. | \_\_:\_\_ | Set stirring rate:  .................. RPM |  |
|  | Thiophene is added **carefully** to reaction mixture. **Exothermic reaction occurs (expected during portions 1 and 2).** Temperature of reaction mixture (measured with 003-209) should be in range 55‑65 ⁰C. Once temperature of reaction mixture reaches **60 ⁰C, stop the addition** of thiophene and wait until temperature of reaction mixture is back to 55 ⁰C. Fill Table 4 below.  **NB! 65⁰C – The upper limit of the temperature of reaction mixture during addition of thiophene is CRITICAL parameter.**  **1st portion is added slowly, ~70g/min;**  **The rest is added quickly while keeping the temperature of reaction mixture below +65°C.**  Optimal time of addition is 1....1.5 hours.  Each portion of thiophene is to be charged sequentially by repeating operations 11, 12 and 13.  Expected behaviour of reaction mixture: exothermic reaction with set-off when about 25-35% of all thiophene is added, gradual decrease of viscosity of reaction mixture. | Addition started:  \_\_:\_\_  All thiophene is added:  \_\_:\_\_ |  |  |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 4 – ADDITION OF THIOPHENE** | | | | | | | | | | | | Temperature of reaction mixture should be in range +55…+65⁰C. Once temperature of reaction mixture reaches **60 ⁰C, stop the addition** of thiophene and wait until temperature of reaction mixture is back to 55 ⁰C. Checks are to be performed in every 2 to 5 minutes. | | | | | | | | | | | | **Portion 1 - ……………… kg (25 % of total amount).**  **Expected time of addition is 15-22 min (SLOW to MODERATE RATE).** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, 003-209, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | | | | |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 4 – ADDITION OF THIOPHENE continues** | | | | | | | | | | | | **Portion 2 - ……………… kg (25 % of total amount).**  **Expected time of addition is 10-22 min (prevent from heating over 65 °C).** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, 003-209, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | | | | |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 4 – ADDITION OF THIOPHENE continues** | | | | | | | | | | | | **Portion 3 - ……………… kg (25 % of total amount).**  **Expected time of addition is 8-11 min (FAST RATE, prevent from heating over 65 °C).** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, 003-209, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | | | | |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 4 – ADDITION OF THIOPHENE continues** | | | | | | | | | | | | **Portion 4 - ……………… kg (25 % of total amount).**  **Expected time of addition is 8-11 min (FAST RATE, prevent from heating over 65 °C).** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, 003-209, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | | | | |
|  | After addition of thiophene is finished, if the temperature went below +55⁰C bring reaction temperature to +55⁰C, for that, temperature of jacket is first set to 70 ⁰C and then reduced to 55⁰C and reaction is continued for 6.0-6.5 hours.  Stirring rate is reduced to 100-150 RPM (recommended). Temperatures of reaction mixture and of jacket are recorded into Table 5; **check every 15-20** **min**. Operations 19-21 are done in parallel. | Start:  \_\_:\_\_  Finish:  \_\_:\_\_ | Temperature setting:  ................ oC  Stirring setting  ................... RPM |  |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 5 – STIRRING OF REACTION MIXTURE** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | | | | |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 5 – STIRRING OF REACTION MIXTURE continues** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | | | | |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 5 – STIRRING OF REACTION MIXTURE continues** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | | | | |
|  | 42% KOH solution is prepared according to the procedure described in Table 1.2. | \_\_:\_\_ |  |  |
|  | Saturated NaCl solution is prepared according to the procedure described in Table 1.3. | \_\_:\_\_ |  |  |
|  | Liquid addition system is cleaned:   1. Liquid addition line is disconnected from reactor, directed into jug “Cleaning” 2. ca 0.5 L of acetone for cleaning is charged into dropping funnel; 3. amount of acetone from point 2 is discharged into jug “Cleaning” 4. ca 1 L of RO water for cleaning is charged into dropping funnel; 5. amount of water from point 4. Is discharged into jug “Cleaning” 6. liquid addition line is connected back to reactor | \_\_:\_\_ |  |  |
|  | After the stirring period is finished, temperature of the jacket is set to 10 ⁰C. Wait until actual temperature of the jacket (011-22 RETURN) is 10…25 ⁰C. | Start  \_\_:\_\_  Reached 10…25 ⁰C  \_\_:\_\_ | Temperature setting:  …......... oC  Reached temperature  (011-22 RETURN value):  ............. oC |  |
|  | Dropping funnel of reactor 002-17 is filled with **water for production for quenching**. Portions are about 4-5 kg big, measured first into 5L jug “TILE” and then charged in to dropping funnel using vacuum.  **Specified loading: ..... kg ( ..... – ..... kg)** | \_\_:\_\_ | Warehouse code:  …………….  Measured amount:  portion 1 :  ................... kg  portion 2:  ................... kg  portion 3:  ................... kg  portion 4:  ................... kg  portion 5:  ................... kg  **TOTAL added amount:**  **................... kg** |  |
|  | Water for quenching is carefully added to the reaction mixture. Recommended stirring set 200‑220rpm. Temperature of mixture is held in range 40-60 ⁰C.  Addition process has significant exothermic effect in the beginning, smaller exotherm in the end.  **Pause the addition once temperature of reaction mixture is +60⁰C and wait until temperature is back to +55⁰C**  Temperatures of reaction mixture and of jacket are documented in Table 6 every 10 min. | Addition started:  \_\_:\_\_  Addition finished:  \_\_:\_\_ |  |  |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **TABLE 6 – QUENCHING OF REACTION MIXTURE** | | | | | | | | | | | | Time  (HH:MM) | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | \_\_:\_\_ | | Reaction mixture temperature, oC |  |  |  |  |  |  |  |  |  |  | | Thermostat temperature setting, oC |  |  |  |  |  |  |  |  |  |  | | Stirring set, rpm |  |  |  |  |  |  |  |  |  |  | | | | | |
|  | After addition of water is finished the temperature of the jacket is set to 60⁰C and reaction mass is stirred for 40….60 min.  Temperature of reaction mixture (reading of 003-209) should be in range 40-60⁰C. Record the actual temperature in the end of operation. | Stirring started:  \_\_:\_\_  Stirring finished:  \_\_:\_\_ | 003-209 reading in the end of stirring:  ............... ⁰C |  |
|  | Stirring is set to 5-15 RPM and layers are allowed to separate. Wait at least 30 minutes.  Expected time: 30-45 min. | Start of separation of phases:  \_\_:\_\_  Phases are separated:  \_\_:\_\_ | Are the phases separated:  Yes: ⬜  No: ⬜  Appearance of reaction mixture:  ……………………… |  |
|  | **Stop stirring completely.** Aqueous phase (lower phase) is discharged into canisters ‘AQUEOUS WASTE’ through the bottom valve. Use flashlight to check phases separation.  Additionally, the canister must be marked “ACIDIC WASTE, DO NOT MIX WITH OTHER WASTE”.  *Alternatively connect peristaltic pump, open the bottom valve completely and use the pump to control the draining, slowing down at the end. Use clear view in bottom pipe to check for phase separation. In the beginning set peristaltic pump to 50-80% of speed, at the end lower it to 10-5% to get complete separation.* | \_\_:\_\_ | Discharged mass:  1. ………….. kg  2. ………….. kg  3. ………….. kg |  |
|  | Stirring is started, recommended 140-150 rpm. | \_\_:\_\_ | Setting: ………….RPM |  |
|  | Temperature of the jacket is set to 10 ⁰C. Wait until actual temperature of the jacket (011-22 RETURN) is 10…25 ⁰C. | Start  \_\_:\_\_  Reached 10…25 ⁰C  \_\_ : \_\_ | Temperature setting:  …......... oC  Reached temperature  (011-22 RETURN value):  ............. oC |  |
|  | 42% **KOH** solution is charged into reactor using funnel „TILE reactor“  **NB! The addition is portion-wise, to keep the temperature below +65°C.**  Approximate portion size is 1-2kg.  **Specified loading: ..... kg ( ..... – ..... kg)**  After addition is complete, temperature of reaction mixture (003-209) is registered | Started addition  \_\_:\_\_  Finished  \_\_:\_\_ | Measured amount:  ........... kg  003-209 reading in the end of addition  ............. oC |  |
|  | Reaction mixture is stirred for 10-15 min, then pH is checked with pH indicator paper. pH should be basic, **(>12).**  **If required, pH is adjusted with addition of solid 85% KOH.**  **Optional**, use a pH meter 005-8 or analogue for checking the pH. | Stirring started:  \_\_:\_\_  Adjust-ment complete:  \_\_:\_\_ | Approximate pH of reaction mixture after adjusting  pH ……..  Additional 85% KOH amount:  …………. kg |  |
|  | Reaction mixture is left stirring at temperature +55…+60⁰C overnight (8-14 hours). Recommended stirring rate is 140…160 RPM. Reflux condenser is left working. | End of stirring:  \_\_:\_\_ | Setting:  ………….RPM |  |
|  | Waste canisters are weighed and removed from the room. Waste amount is recorded in Table 9.1. |  | ……………….. kg  (Op. 25) |  |
|  | Cleaning of used auxiliary equipment (spoons, shovels, funnels, jugs, thermometers) and working surfaces is done according to Table 3. | Finished at:  \_\_:\_\_ |  |  |

| **No.** | | **Description** | **Parameters** | | Operator’s signature  Veri­fier’s signature |
| --- | --- | --- | --- | --- | --- |
| **Time** | **Other** |
| **3rd working day \_ \_ . \_ \_ . \_ \_ \_ \_**  Temperature of room 257-2 has been registered in room logbook. | | | | |  |
|  | Saturated **NaCl solution for dilution** is measured with jug by weighing on balances 007-42 and charged into reactor using funnel “TILE reactor”  Keep temperature setting +50…+60°C till the end of op.41  **Specified loading: ….. kg ( ….. – ….. kg)** | | \_\_:\_\_ | Measured amount:  ….......... kg |  |
|  | The mixture in the reactor 002-17 is stirred for 8…12 minutes. | | Start of stirring  \_\_:\_\_  End of stirring  \_\_:\_\_ | Are the phases completely mixed:  Yes: ⬜  No: ⬜  Stirring rate:  .............. RPM |  |
|  | **Stirring is set to 5-15 RPM.** Layers are allowed to separate.  **Expected separation time is 40 – 120min** | | Start of separation of phases:  \_\_:\_\_  Phases are separated:  \_\_:\_\_ | Are the phases separated:  Yes: ⬜  No: ⬜ |  |
|  | **Stirring is stopped.** Aqueous phase (lower phase) is discharged into canisters ‘AQUEOUS WASTE’ through the bottom valve.  **NB! Expect problematic separation. This operation requires extra attention to get clean cut of phases.**  *Alternatively connect peristaltic pump, open the bottom valve completely and use the pump to control the draining, slowing down at the end. Use clear view in bottom pipe to check for phase separation. In the beginning set peristaltic pump to 50-80% of speed, at the end lower it to 10-5% to get complete separation.*  Additionally, the canister must be marked “BASIC WASTE, DO NOT MIX WITH OTHER WASTE”. | | \_\_:\_\_ | Discharged mass:  1 …………………kg  2 …………………kg  3 …………………kg |  |
|  | **NaCl solution for rinsing** is measured with jug by weighting on balances 007-42 and charged into reactor using funnel “TILE reactor”  **Specified loading: ..... kg ( ..... – ..... kg)** | | \_\_:\_\_ | Measured amount:  ............. kg |  |
|  | The mixture in the reactor 002-17 is stirred for 8…12 minutes. Suggested stirring rate is 180‑220 RPM | | Start of stirring  \_\_:\_\_  End of stirring  \_\_:\_\_ | Are the phases completely mixed:  Yes: ⬜  No: ⬜  Stirring rate:  .............. RPM |  |
|  | Stirring is set to 5-15 RPM and layers are allowed to separate for at least 60 min. | | Start of separation of phases:  \_\_:\_\_  Phases are separated:  \_\_:\_\_ | Are the phases separated:  Yes: ⬜  No: ⬜ |  |
|  | **Stirring is stopped.** Aqueous phase (lower phase) is discharged into canister ‘AQUEOUS WASTE’ through the bottom valve. | | \_\_:\_\_ | Discharged mass:  1 …………………kg  2 …………………kg  3 …………………kg |  |
|  | Thermostat 011-22 is switched off. Tap water for condenser is switched off. | | \_\_:\_\_ |  |  |
|  | Canister(s) for TILE IP.1, crude product are weighted on balance 007-42, tare weight is documented into Table 7 – Part 2. | | \_\_:\_\_ |  |  |
|  | Upper phase of extraction – IP.1 crude product - is discharged into canister(s) using funnel “TILE IP.1, crude”. | | \_\_:\_\_ | Canisters are clean after discharging: ⬜ |  |
|  | Samples for analysis and retention are taken from the product according to sampling procedure.  Sampling protocol (QD-LC) and Table 7 – Part 1 are filled. Photocopies of labels are taken. | | \_\_:\_\_ | Sampling protocol is filled: ⬜  Photocopies are taken:  ⬜ |  |
|  | Primary package of the product (canister(s)) is closed and labelled. Photocopies of labels are taken. Table 7 – Part 2 is filled. | | \_\_:\_\_ | Photocopies are taken:  ⬜ |  |
|  | Yield of process is calculated:  **Calculated amount:** | | \_\_:\_\_ | IP.1, crude sum of packed product  (Table 7-Part 2):  =…………… kg  Calc. amount:  =  =…………… kg  Yield:  …………% |  |
|  | Waste canisters are weighed and removed from the room. Waste amount is recorded in Table 9.1. | | \_\_:\_\_ | .................. kg  (Op.36 + Op.40) |  |
|  | All used apparatus is clean (see Table 3). | | \_\_:\_\_ |  |  |

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| **TABLE 7** | | | | | | | | |
| **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** |
| **Glass vial 1: for analysis**  **(2 to 3 g)** |  | |  |  | ⬜ | | ⬜ |  |
| **Glass vial 2: for retention**  **(4 to 6 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** |
| **Canister 1: Product** |  |  | |  | ⬜ | ⬜ | |  |
| **Canister 2: Product**  ⬜ not used |  |  | |  | ⬜ | ⬜ | |  |
| **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).  **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.)** | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ |  |
| Photocopies of labels are added to respective fields in **Table 8 (PM is responsible).** | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ |  |
| Thermostat log is reviewed. | **\_ \_.\_ \_.\_ \_ \_ \_**  \_\_:\_\_ |  |

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| **TABLE 8 – EXAMPLES OF THE LABELS** | |
| For **SAMPLES** | |
| Template of the label:   |  | | --- | | **Cyclopentyl 2-thienyl ketone, crude**  **(TILE IP.1, crude)**  **ANALYSIS**  Batch No: TBD-0322-X, IP.1 crude  **Date:** ..............................................  **Sample amount:** ............................  **Operator’s signature:** ....................  **Storage conditions:** not exceeding 30°C | | Used label (photo-copy): |
| |  | | --- | | **Cyclopentyl 2-thienyl ketone, crude**  **(TILE IP.1, crude)**  **RETENTION**  Batch No: TBD-0322-X, IP.1 crude  **Date:** ..............................................  **Sample amount:** ............................  **Operator’s signature:** ....................  **Storage conditions:** not exceeding 30°C | | Used label (photo-copy): |

|  |  |
| --- | --- |
| For **PRODUCT** | |
| Template of the label:   |  | | --- | |  | | Used label (photo-copy): |
|  |  |

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| **TABLE 9.1 – OBTAINED MATERIALS** | | | | |
| **Product** | | | | |
| **Name** | **Calculated amount [kg]** | **Actual amount**  **[kg]** | **Calculated yield**  **[%]** | **Signatures** |
| Cyclopentyl 2-thienyl ketone, crude  (TILE IP.1, crude) | See Op. 46 | See Table 7-Part 2 | See Op. 46  Expected: 80-85% | **PM** |
| **Waste** | | | | |
| **Name** | **Category** | **Actual amount**  **[kg]** | **Destination** | **Signatures** |
| **Aqueous Waste (Op. 25)** | II  Additional label “ACIDIC - DO NOT MIX WITH OTHER WASTE” |  | Discarded | **Operator**  **PM** |
| **Aqueous Waste (Op. 36)** | II  Additional label “BASIC - DO NOT MIX WITH OTHER WASTE” |  | Discarded |
| **Aqueous Waste (Op. 40)** | II |  | Discarded |
| **Material loss** |  |  |  |
| **TOTAL AMOUNT:** | |  |  |

**\*Material loss = total loaded amount – product actual amount – wastes actual amounts.**

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| **TABLE 9.2 – UNUSED MATERIALS AND SOLUTIONS** | | | | |
| **Name** | **Leftover amount [g]** | **Operator’s signature** | **Destination**  **(decision of PM)** | **PM’s signature** |
|  |  |  | □ **discarded**  □ other:  ........................... |  |

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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:**

|  |  |  |  |
| --- | --- | --- | --- |
| **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):**