Table 3.1.1.1. *Survey of crystallization techniques suitable for the crystallization of low-molecular-weight organic compounds for X-ray crystallography (adapted from van der Sluis, Hezemans & Kroon, 1989)*

| Technique | Advantage(s) | Limitation(s) |
|---|---|---|
| Evaporation from a single solvent | Simple<br>Inexpensive | Limitation to solvents with adequate vapour pressure<br>Crust formation on tube walls<br>Crystals that are dried are less suitable as seeds, may lose included solvent and become tightly adhered to the crystallization vessel<br>Difficult to reproduce<br>Limited number of solvents give concentration 5–200 mg $ml^{-1}$ for a particular compound |
| Evaporation from a binary mixture of solvents (volatile solvent and non-volatile precipitant) | No crust formation on the tube walls<br>Crystals are not dried | Stringent demands on solubility, miscibility and volatility of the two solvents<br>Difficult to reproduce |
| Batch crystallization | No demands on the volatility of the solvent or precipitant<br>Repeated seeding by thermal treatment is easy | Metastable zone with regard to supersaturation must be large<br>High and almost uncontrollable crystallization rate<br>Solvents must be miscible |
| Liquid–liquid diffusion | Favourable change in supersaturation at the interface during crystallization<br>Repeated seeding by thermal treatment is easy | Density differences required for the two liquids (less stringent if capillaries are used)<br>Viscosity of the liquids greater than water<br>Solvents must be miscible<br>High and almost uncontrollable crystallization rate |
| Sitting-drop vapour-phase diffusion | Crystallization rate can easily be controlled by changing the diffusion path, solvent, precipitant, or pH<br>Repeated seeding easily implemented<br>Highest number of independent variables to obtain wide variety of conditions | Solvents must be miscible<br>Solvent preferably less volatile than precipitant |
| Hanging-drop vapour-phase diffusion | Crystallization rate can easily be controlled by changing solvent, precipitant, or pH<br>Easy examination of crystallization outcome in array-like set-up | Only applicable in case of water-based solvents<br>Diffusion rate is fast and difficult to control<br>See previous method |
| Temperature change | Easily controllable parameter<br>Repeated seeding extremely easily and accurately carried out<br>With Dewar flask inexpensive and simple | Limited to thermally stable compounds and (pseudo)polymorphs |
| Gel crystallization | Suited for sparingly soluble or easily nucleating compounds | Limited variety of solvents possible<br>Sampling of crystals difficult<br>Laborious |
| Sublimation | No inclusion of solvent of crystallization | Limited to small hydrophobic molecules<br>Laborious |
| Solidification | For liquids and gases the only applicable method | Limited to thermostable compounds<br>High change of amorphicity<br>Laborious |





references