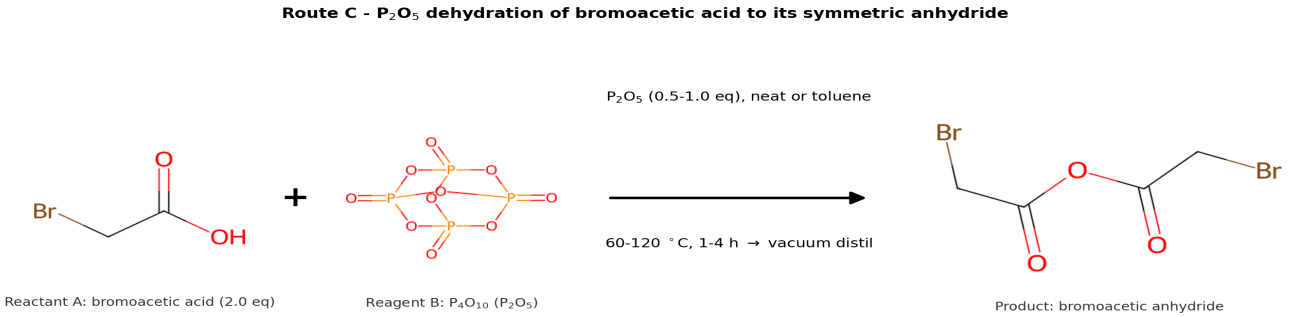
Bromoacetic Anhydride — Reaction Condition Recommendation

Route C dehydration: bromoacetic acid (2 eq) + P_2O_5 → bromoacetic anhydride | Generated: 2026-06-14 | Source: BookRAG (Clayden) + Crossref-verified literature (Burton & Kaye, *Synth. Commun.* 1989; Lu et al., *ACS Omega* 2022). Companion to 13094-51-4_synthesis_routes.pdf, Route C.

Strategy note: the target is a symmetric carboxylic-acid anhydride, so the disconnection is a single dehydrative condensation of two molecules of bromoacetic acid: 2 $BrCH_2CO_2H$ → $(BrCH_2CO)_2O$ + H_2O. Phosphorus pentoxide (P_4O_{10}, "P_2O_5") is the classical, cheap dehydrating agent: it sequesters the liberated water as phosphoric/polyphosphoric acid, driving the equilibrium to the anhydride. The anhydride (bp 226 °C/760 mmHg) is then isolated by vacuum distillation away from the non-volatile phosphate residue. Anhydride-from-acid dehydration is not robustly templated in reaction-condition neural networks (ASKCOS / Reaxys-trained models) — conditions are therefore sourced from textbook chemistry and Crossref-verified literature rather than from an NN prediction. Option B (acetic-anhydride exchange) is given as a cleaner alternative, with the caveat that acetic anhydride is a DEA List II / EU Cat-2 controlled precursor.

Substrate-specific warning: bromoacetyl species are potent alkylating agents and lachrymators. Do NOT use amine bases (pyridine, Et_3N, DMAP) anywhere in this chemistry — they are N-alkylated/quaternised by the α-bromo carbonyl and consumed, and they generate coloured quaternary-salt impurities. Both recommended methods below are deliberately base-free. The product hydrolyses on contact with moisture back to bromoacetic acid; exclude water throughout and store cold under N_2.

Reaction Scheme



Role	Name	SMILES	MW	Formula
Reactant A (substrate, 2.0 eq)	Bromoacetic acid (CAS 79-08-3; used 2.0 eq)	OC(=O)CBr	138.95	$C_2H_3BrO_2$
Reagent B (dehydrating agent)	Phosphorus pentoxide, P4O10 (CAS 1314-56-3; dehydrating agent)	O=P12OP3(=O)OP(=O)(O1)OP(=O)(O2)O3	283.89	$O_{10}P_4$
Product (symmetric anhydride)	Bromoacetic anhydride (CAS 13094-51-4)	O=C(CBr)OC(=O)CBr	259.88	$C_4H_4Br_2O_3$

Conditions Sourcing — Literature & BookRAG

P_2O_5 dehydration of carboxylic acids to symmetric anhydrides (2 RCO_2H → $(RCO)_2O$) is textbook chemistry. The most practical literature protocol is the **"supported P_2O_5" reagent of Burton & Kaye (*Synth. Commun.* 1989, 19, 3331)**: P_2O_5 dispersed on an inert mineral support, refluxed with the acid in toluene — e.g. anisic acid → anisic anhydride in 69 % isolated yield. Simple aliphatic acids such as bromoacetic acid typically give higher conversions. The acetic-anhydride

exchange route (Option B) is “very general” for anhydrides whose product boils above acetic acid (Clayden, *Organic Chemistry*; ScienceDirect / OpenStax anhydride reviews). Both options are validated at multi-kilogram scale.

Recommended Conditions — Option A: P_2O_5 dehydration (primary, Route C)

Parameter	Setting	Notes
Dehydrating agent	P_4O_{10} (“P_2O_5”), 0.5–1.0 eq per anhydride	Stoichiometrically P_4O_{10} can absorb up to 6 H_2O (→ 4 H_3PO_4), so only ~0.2 eq is needed on paper; in practice 0.5–1.0 eq is charged because solid-phase mixing is poor and the phosphoric/polyphosphoric intermediates are weaker dehydrants. A **silica/Celite-supported P_2O_5** reagent (Burton & Kaye) gives cleaner mixing and easier filtration.
Solvent	Neat melt, or anhydrous toluene / CH_2Cl_2 (supported-reagent variant)	Neat is simplest at scale. The supported-P_2O_5 + toluene reflux variant is milder and avoids a thick phosphate cake. Solvent must be rigorously dry.
Temperature / time	60–120 °C, 1–4 h (toluene reflux 111 °C for the supported variant)	Mixing P_2O_5 with the acid is exothermic; add P_2O_5 portionwise with cooling. Hold until water uptake / conversion is complete (IR loss of the broad acid O–H; appearance of the anhydride C=O doublet ~1820 & 1750 cm^{-1}).
Order of addition	Charge bromoacetic acid (± solvent); add P_2O_5 in portions over 20–60 min with cooling	Never add water/wet acid to a P_2O_5 bulk — the hydration is violent. Keep the pot < 60 °C during addition, then heat to drive the dehydration.
Atmosphere	Dry N_2, anhydrous throughout	Both P_2O_5 and the product anhydride react with moisture. Trace water regenerates bromoacetic acid and consumes the dehydrating agent.
Isolation / purification	Vacuum-distil the anhydride away from the phosphate residue (bp 226 °C/760 mmHg — distil at reduced pressure, ~10–20 mmHg, to hold the pot temperature moderate).	Distillative isolation gives high purity with no chromatography (the anhydride hydrolyses on silica). Reduced pressure limits thermal stress on the α-bromo anhydride and avoids darkening. Residue is a corrosive phosphoric-acid sludge — neutralise before disposal.
Expected yield	~70–88 % after distillation	Literature anchor: supported P_2O_5 gave anisic anhydride at 69 % (Burton & Kaye); simple aliphatic acids generally run higher. Losses are mainly distillation hold-up and residual mono-acid in the sludge.

Recommended Conditions — Option B: acetic-anhydride exchange (cleaner alternative)

Parameter	Setting	Notes
Dehydrating agent	Acetic anhydride (Ac_2O), 1.05–1.3 eq per anhydride (i.e. per 2 acids)	Net: 2 $BrCH_2CO_2H$ + Ac_2O → $(BrCH_2CO)_2O$ + 2 AcOH. Slight excess Ac_2O drives conversion. **Ac_2O is a DEA List II / EU Category-2 controlled drug precursor** — record-keeping and reporting apply at scale.
Solvent	Neat (no added solvent)	The reaction is run neat and driven by distillation; added solvent only complicates the cut between AcOH and product.
Base / catalyst	None (base-free). No amine catalyst.	Unlike typical sulfation/acylation, **do not add pyridine/DMAP/Et_3N** — the α-bromo carbonyl alkylates them. A trace of a strong protic acid (e.g. H_2SO_4, < 1 mol%) can accelerate exchange if needed but is usually unnecessary.

Temperature / time	Heat 100–150 °C while distilling off AcOH (bp 118 °C); then reduce pressure (~30 mmHg) to strip residual acetic species; 3–8 h total.	The driving force is removal of the lower-boiling acetic volatiles (AcOH 118 °C, Ac_2O 139 °C); the high-boiling bromoacetic anhydride (226 °C) remains in the pot. Keep temperature as low as the distillation allows to protect the α-bromo product.
Order of addition	Combine bromoacetic acid + Ac_2O; heat to distil AcOH from the outset	No portionwise/exotherm concerns as with P_2O_5. Fit an efficient fractionating column to separate AcOH cleanly from the product.
Atmosphere	Dry N_2	Exclude moisture (hydrolysis to the acid). AcOH is removed as distillate.
Isolation / purification	After acetic species are fully stripped, the pot residue is the product; optionally short-path vacuum-distil for high purity.	**Key impurity = the mixed anhydride** $BrCH_2CO–O–COCH_3$. If acetic species are not exhaustively removed the product is contaminated with this mixed anhydride — monitor by ^{1}H NMR (acetyl CH_3 singlet ~2.2 ppm) and continue stripping until absent.
Expected yield	~80–90 % isolated	Cleaner crude profile than Option A (no phosphate sludge) but the controlled-precursor status of Ac_2O and the mixed-anhydride impurity risk are the trade-offs.

Chemistry Notes & Risks

Why P_2O_5 works and how much to use. P_2O_5 is a thermodynamic water sink: it converts the reversible 2 RCO_2H ⇌ $(RCO)_2O$ + H_2O into an irreversible process by hydrating to phosphoric/polyphosphoric acid. The theoretical charge is small (~0.2 eq P_4O_{10} absorbs the one equivalent of water), but in practice 0.5–1.0 eq is used to overcome poor solid-liquid mixing and the diminishing dehydrating power of the partially-hydrated phosphate.

Thermal stability of the α-bromo anhydride. Bromoacetic anhydride has no β-hydrogen, so it cannot undergo E2 HBr-elimination; it is thermally robust enough to distil. However, prolonged heating of any α-halocarbonyl promotes darkening and slow decomposition — therefore distil under **reduced pressure** (Option A) and keep pot temperatures as low as the separation permits (Option B).

Mixed-anhydride impurity (Option B). Acetic-anhydride exchange proceeds through the mixed anhydride $BrCH_2CO–O–COCH_3$. Complete removal of all acetic species (AcOH + Ac_2O) by distillation is what pulls the equilibrium to the symmetric product; incomplete stripping leaves mixed anhydride. Track the acetyl CH_3 singlet (~2.2 ppm, ^{1}H NMR) to confirm the cut is clean.

No amine bases. This is the single most important substrate-specific caution. Bromoacetyl groups are powerful SN2 alkylators; pyridine, Et_3N, DMAP and similar nucleophilic amines are quaternised (forming e.g. pyridinium-acetate salts), consuming reagent and colouring the product. Keep the entire sequence base-free.

Moisture sensitivity / hydrolysis. The product reverts to bromoacetic acid on contact with water. Use anhydrous reagents and glassware, blanket with dry N_2, and store the isolated anhydride cold (< 0 °C) under inert gas. Do not attempt aqueous workup or silica chromatography.

Reagent hazards. P_2O_5 is corrosive and reacts violently with water (add portionwise, cool). Bromoacetic acid is acutely toxic by all routes (GHS H300/H310/H330) and corrosive (H314); bromoacetic anhydride is a potent lachrymator / vesicant / alkylating agent. Use closed transfer, fume containment and full PPE (face shield, butyl/nitrile gloves).

Quality control. Confirm by ^{1}H NMR ($BrCH_2$ singlet ~3.9–4.0 ppm; absence of acetyl CH_3 ~2.2 ppm and of acid O–H); IR (anhydride C=O doublet ~1820 and 1750 cm^{-1}, plus C–O–C ~1040 cm^{-1}); GC for residual bromoacetic acid / acetic species; Karl Fischer for water. mp 34–42 °C, bp 226 °C/760 mmHg, density ~2.14 g/cm^3 (lit.).

References

1. Burton, S. G.; Kaye, P. T. A Convenient Preparation of Carboxylic Acid Anhydrides Using a “Supported” Phosphorus Pentoxide Reagent. *Synth. Commun.* **1989**, *19* (19), 3331–3335. DOI: 10.1080/00397918908052736. (Primary protocol for Option A; anisic acid → anisic anhydride, 69 %.) [Crossref-verified]

2. Lu, X.; Fan, Y.; Liu, J.; Sun, L. A Facile Synthetic Method for Anhydride from Carboxylic Acid with the Promotion of Triphenylphosphine Oxide and Oxalyl Chloride. *ACS Omega* **2022**, *7* (38), 34352–34358. DOI: 10.1021/acsomega.2c03991. (Mild, base-free alternative dehydration method; useful when distillative isolation is undesirable.) [Crossref-verified]

3. Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd ed.; Oxford University Press: Oxford, 2012. (Acid + acid chloride → anhydride; acetic-anhydride dehydration as a general route to anhydrides whose product boils above acetic acid — basis for Option B; pp. ~229, 633.)

4. Physical-property data for bromoacetic anhydride (CAS 13094-51-4): mp 34–42 °C, bp 226 °C/760 mmHg, density 2.14 g/cm^3, white-to-brown solid — ChemicalBook / Chemsrc compiled supplier data and Thermo Scientific (Alfa) product listing. [web-verified]

5. Säurefabrik Schweizerhall (Gallegra, P.; Degischer, G.). Process for the preparation of acid anhydrides. US Patent 5,292,949, 1994. (Industrial symmetric-anhydride process via acid *halide* + acetic anhydride with distillative removal of the acetyl halide — the acyl-halide route, cross-referenced from Route B; NOT the free-acid Ac_2O exchange of Option B.) [title/scope verified on Espacenet/Google Patents]