

Supporting Information

Solid-phase Synthesis of Tertiary *N*-Methyl Amines Including Tropanes

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Experimental Procedures

General procedure for anchoring nortropinone on the Merrifield, Trityl chloride and Wang *p*-nitrophenylcarbonate resins (Table 1):

To a solution of nortropinone (**1**, 22 mmol, 5 equiv) in DCM or DMF (30 mL) was added Merrifield resin (4 g, 1.2 mol/g, 4.4 mmol), Trityl chloride resin (2.44 g, 1.8 mmol/g, 4.39 mmol) or Wang *p*-nitrophenylcarbonate resin (5.16 g, 0.85 mmol/g, 4.39 mmol, prepared from Wang gel, Fluka, 1% PS-DVB, 200-400 mesh, 1.0 mmol/g) and the mixture was agitated at rt or 80 °C (see Table 1) for 48 h. Then the polymer was washed successively with methanol (2 × 15 mL), DCM (2 × 15 mL), DMF (2 × 15 mL), methanol (2 × 15 mL), DCM (3 × 15 mL) and methanol (3 × 15 mL). The residual solvent was removed from the gel *in vacuo* and the gel was dried to a constant mass (2-16 h) under high vacuum to give a yellow or slightly off-white powder.

All resulting polymers had similar spectral characteristics (IR and ¹³C-NMR). Loadings of the polymers were determined gravimetrically from mass of triethylamine hydrochloride according to the described procedure¹ and are shown in Table 1.

Representative polymers:

(Nortropan-3-one-8-yl)carbonyloxymethylpolystyrene (4) (0.87 mmol/g, 100% of the theoretical loading). $\nu_{\max}(\text{KBr})$ 1710 (C=O) cm^{-1} ; δ_{C} (50.3 MHz, CDCl_3) 207.8, 154.0, 114.9, 67.1, 53.2, 48.8, 29.8.

(Nortropan-3-one-8-yl)methylpolystyrene (6) (1.07 mmol/g, 99% of the theoretical loading). $\nu_{\max}(\text{KBr})$ 1771 (C=O) cm^{-1} ; δ_{C} (50.3 MHz, CDCl_3) 210.2, 58.4, 54.8, 48.2, 27.9; Anal. found: C, 87.92; H, 7.82; N, 1.58.

General procedure for immobilization of nortropinone on triazene polymer with *para*-C₃-T2 linker (5):

The triazene polymer,² 3-[4-(3,3-diethyltriaz-1-enyl)phenoxy]propyloxymethylpolystyrene (0.70 g, 0.88 mmol/g) was swollen in DCM (5 mL), cooled to -10 °C and washed with a cold solution of TFA (2 × 3 mL, 10 min. 10% TFA/DCM) followed by DCM (4 × 3 mL). Then a solution of nortropinone (0.78 g, 6.24 mmol, 10.1 equiv) in DCM (6 mL) was added and the suspension was agitated for 1h at -10 °C, warmed up to room temperature, and agitated for 12 h. Then the polymer was washed with methanol (2 × 5 mL), DCM (2 × 5 mL), DMF (2 × 5 mL), THF (2 × 5 mL), methanol (2 × 5 mL), DCM (2 × 5 mL), methanol (2 × 5 mL) and dried under high vacuum to a constant mass to give a red powder.

3-[4-(Nortropan-3-one-8-ylazo)phenoxy]propyloxymethylpolystyrene (5) (0.71 mmol/g, 78% of the theoretical loading). $\nu_{\max}(\text{KBr})$ 1713 (C=O) cm^{-1} ; δ_{C} (50.3 MHz, CDCl_3) 207.3, 158.0, 134.3, 122.1, 115.0, 67.5, 65.0, 54.9, 47.5, 29.8, 26.9; Anal. found: C, 85.25; H, 7.88; N, 2.38.

General procedure for cleavage of nortropinone from polymeric supports 3, 4 and 5:

To a swollen in DCM (3 mL) polymeric gel **3**, **4** or **5** (0.30 g), was added a solution of trifluoroacetic acid in DCM (3 mL, 20% TFA/DCM for **3** and **4**, and 10% TFA/DCM cooled to 0 °C for **5**). After 30 min for **3** and **4**, and 10 min for **5**, the gel was washed with DCM (2 × 4 mL), the treatment with the trifluoroacetic acid solution was repeated and the polymers were washed six times, alternately with DCM and methanol (4 mL of each solvent). The collected combined washings were concentrated *in vacuo* to give crude product trifluoroacetate. Loadings of the cleaved amine (see Table 1) were calculated from the mass of hydrochloride produced by treatment of the trifluoroacetates with conc. hydrochloric acid, evaporation of volatiles and high vacuum drying. Purity and identity of the product were confirmed by ¹H-NMR analysis.

General procedure for cleavage of nortropinone from methylpolystyrene (6):

To a swollen in 1,2-dichloropropane (3 mL) gel **6** (0.30 g), was added a solution of 1-chloroethyl chloroformate (0.36 mL, 0.472 g, 33 mmol, 10 equiv) in 1,2-dichloropropane (3 mL) and the suspension was shaken intermittently for 24 h. Then the gel was washed six times, alternately with DCM and methanol (4 mL of each solvent). The collected combined washings were concentrated *in vacuo*, taken up in methanol (6 mL) and left for 48 h at rt or refluxed for 12 h. Evaporative removal of volatiles and high vacuum drying gave nortropinone in the form of hydrochloride. Loadings of cleaved nortropinone (see Table 1) were calculated from the mass of the obtained hydrochloride.

General procedure for immobilization of amines including nortropinone on the Wang resin (7):

Wang resin (1.20 g, Fluka 1.00 mmol/g, 200-400 mesh) was swollen in dry DCM (5 mL), filtered from DCM and suspended in a new portion of dry DCM (5 mL). The suspension was agitated at 0 °C while thionyl chloride (0.45 mL, 6 mmol, 5 equiv) was added. After 1 h the mixture was filtered and the resin was rinsed at 0 °C with dry DCM (3 × 5 mL), MeOH (2 × 5 mL, fast), dry DCM (5 mL), and then at rt with DCM (2 × 5 mL). The resin was suspended in DCM (5 mL), amine (e.g. nortropinone or nortropine, 4 equiv) was added and the mixture was agitated at rt for 48 h. Then the resin was filtered and rinsed with DCM (3 × 5 mL), MeOH (2 × 5 mL), THF (2 × 5 mL), MeOH (2 × 5 mL) and DCM (2 × 5 mL). The resin was dried under vacuum to a constant mass.

Representative polymer:

4-[(Nortropan-3-one-8-yl)methyl]phenoxyethylpolystyrene (7) Nortropan-3-one *N*-anchored on the Wang polymer, (0.79 mmol/g, 90% of the theoretical loading). $\nu_{\max}(\text{KBr})$ 1711 (C=O) cm^{-1} ; δ_{C} (50.3 MHz, CDCl_3) 210.5, 58.4, 54.8, 48.2, 27.9 .

Quantification of loading of amines immobilized on the resin 6, 7, 8, 9, 10:

A sample of the resin was washed successively with a mixture (1:1) of 10% HCl/MeOH (2 × 5 mL), a mixture (1:1) of 10% HCl/THF (2 × 5 mL), mixture (1:1) of 10% HCl/MeOH (2 × 5 mL), MeOH (2 × 5 mL), THF (2 × 5 mL), MeOH (2 × 5 mL) and DCM (2 × 5 mL). The filtrates were rejected. Then the resin was agitated for 15 min with a mixture of triethylamine (5 mL, 20% Et₃N/DCM) and filtered (agitation repeated three times). Then it was washed successively with: MeOH (2 × 5 mL), DCM (2 × 5 mL), MeOH (2 × 5 mL), THF (2 × 5 mL) and DCM (2 × 5 mL). The resin was dried under vacuum to a constant mass. Collected filtrates of triethylamine and following washes were concentrated under vacuum affording a white solid of triethylamine hydrochloride. Loading of the resin bound amine was calculated with the formula:

$$\text{loading [mmol/g]} = \frac{m_{\text{triethylamine} \cdot \text{HCl}} [\text{mg}]}{M_{\text{triethylamine} \cdot \text{HCl}} \left[\frac{\text{mg}}{\text{mmol}} \right] \cdot m_{\text{resin}} [\text{g}]}$$

Quaternization of amines immobilized on the Wang and the Merrifield resin:

Resin with immobilized amine (0.2 g) was suspended in DCM (5 mL). Methyl iodide (20 equiv) of methyl triflate (10 equiv) was added and the suspension was agitated for 48 h. The resin was filtered and washed with: DCM (2 × 5 mL), MeOH (2 × 5 mL), THF (2 × 5 mL), MeOH (2 × 5 mL), DCM (2 × 5 mL). The resin was dried under vacuum to a constant mass.

Cleavage of tertiary amines from the Wang resin with sodium acetate:

A resin with immobilized quaternary ammonium salt (0.2 g) was suspended in glacial acetic acid (2.0 mL), anhydrous sodium acetate (10 equiv, anhydrous NaOAc was dried by melting and heating before use) was added and the mixture was heated to 100 °C for 48 h. The resin was filtered and washed with:

MeOH (3 × 3 mL), DCM (3 × 3 mL), MeOH (3 × 3 mL), and aqueous NH₃ (5 mL, 25%, 2 × 3 mL). The combined filtrates were alkalized with aqueous NH₃, treated with brine (5 mL) and extracted with DCM (4 × 10 mL). The combined extracts were dried over MgSO₄ and concentrated to give a crude product, which was analyzed with TLC, NMR and GC-MS.

Tropine acetate (3-endo-8-methyl-8-azabicyclo[3.2.1]octan-3-yl acetate):^{3,4} Tropine was anchored on the Wang gel according to the general procedure for immobilization of amines on the Wang resin and the resulting polymer (85% of theoretical loading) was subjected to cleavage with sodium acetate. The crude product (0.195 g, quantitative yield based on loading of tropine, ca.85% purity by NMR and GC) was purified by bulb-to-bulb distillation (ot 100-120°C/ 1 Torr) to give a colorless oil (0.129 g, 69%). ¹H NMR (CDCl₃, 400 MHz): 1.70 (d, *J* = 14.5, 2 H); 1.90-2.16 (m, 6 H); 2.03 (s, 3 H); 2.27 (s, 3 H); 3.08-3.13 (m, 2 H); 4.96 (t, *J* = 5.4, 1 H); ¹³C NMR (CDCl₃, 100MHz): 170.0, 67.2, 59.5, 40.1, 36.3, 25.3, 21.2; *m/z* (EI): 183 (M⁺, 20), 124 (100), 96 (22), 94 (50), 83 (25), 82 (47), 43 (19), 42 (21%).⁵

Cleavage of tertiary amines from the Wang resin with thiophenolate:

A resin with immobilized quaternary ammonium salt was suspended in MeOH (2 mL), sodium thiophenolate (0.264 g, 2 mmol, 10 equiv) was added and the mixture was heated to 60 °C for 72 h. Then the resin was filtered and washed with: MeOH (3 × 3 mL), DCM (3 × 3 mL), MeOH (3 × 3 mL). The collected filtrates were washed with aqueous NH₃ and brine (5 mL + 5 mL), and the aqueous layer was back-extracted with DCM (4 × 10 mL). The combined organic layers were dried over MgSO₄ and concentrated to afford a crude product, which was analyzed by TLC, NMR, and GC-MS.

Cleavage of tertiary amines from the Wang resin with morpholine (adopted⁶):

A resin with immobilized quaternary ammonium salt was suspended in morpholine (2 mL), and the mixture was heated to 70 °C for 48 h. Then the resin was filtered and washed with: MeOH (3 × 3 mL), DCM (3 × 3 mL), MeOH (3 × 3 mL). The collected filtrates were washed with aqueous NH₃ and brine (5 mL + 5 mL), and the aqueous layer was back-extracted with DCM (4 × 10 mL). The combined organic layers were dried over MgSO₄ and concentrated to afford a crude product, which was analyzed with TLC, NMR and GC-MS.

References

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