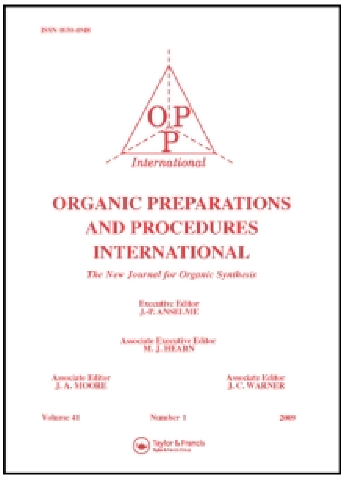

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT ONE STEP SYNTHESIS OF *tert*-BUTYL GLYCINATE AND *tert*-BUTYL SARCOSINATE

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To cite this Article Cavelier, Florine , Rolland, Marc and Verducci, Jean(1994) 'AN EFFICIENT ONE STEP SYNTHESIS OF *tert*-BUTYL GLYCINATE AND *tert*-BUTYL SARCOSINATE', Organic Preparations and Procedures International, 26: 5, 608 — 610

To link to this Article: DOI: 10.1080/00304949409458070

URL: http://dx.doi.org/10.1080/00304949409458070

Anal. Calcd. for $C_7H_7FO_2S$: C, 48.26; H, 4.05. Found: C, 48.35; H, 3.94

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AN EFFICIENT ONE STEP SYNTHESIS OF *tert*-BUTYL GLYCINATE AND *tert*-BUTYL SARCOSINATE

Submitted by
(04/11/94)

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tert-Butyl esters are widely used as an acid-labile protection for carboxylic acids in amino acid and peptide chemistry. Their steric bulk avoids side reactions as diketopiperazine formation and has been shown to be effective in maximizing enantiomeric excesses in the synthesis of optically active amino acids from prochiral starting materials.[1] Due to the poor solubility in organic solvents of glycine and sarcosine, the synthesis of their *tert*-butyl esters by the general method of Roeske[2] and improved by Lawesson et al.[3] are unsuitable. Some preparations of glycine *tert*-butyl ester have been described in the literature *via* two step syntheses. N-Benzyloxycarbonyl glycine, soluble in organic solvents, can be esterified either with isobutene[4] or using *tert*-butanol with DCC/DMAP[5], Boc-F/DMAP[6], or *tert*-butyl bromide with K_2CO_3/benzyltriethylammonium chloride.[7] Other approaches from *tert-butyl* chloroacetate and sodium azide[8] or *tert*-butyl bromoacetate and dibenzylamine[9,10] were used but all these methods required an additional hydrogenation step.

The present work describes the straightforward synthesis of *tert*-butyl glycinate by reaction of the readily available *tert*-butyl bromoacetate with a large excess of ammonia. The reaction proceeds cleanly and in high yield.

$$\mathrm{BrCH_2CO_2tBu} \xrightarrow[\text{(90\%)}]{\text{ether, excess NH}_3} \mathrm{H_2NCH_2CO_2tBu} \xrightarrow[\text{(100\%)}]{\text{HCl, ether}} \underset{\text{Quantitative}}{\mathrm{H_2NCH_2CO_2tBu{\bullet}HCl}}$$

The slow addition of *tert*-butyl bromoacetate to a large excess of liquid ammonia (4ml/mmol) prevents the substitution of the nitrogen atom by two or three molecules of the reagent. *tert*-Butyl glycinate was obtained as a free base ready for use. Alternatively, for storage, it can be treated with dry hydrogen chloride to afford its HCl salt. The same procedure was applied to the preparation of *tert*-butyl sarcosinate by using methylamine in place of ammonia.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Brüker WP 80/CW spectrometer using TMS as an internal standard. Mass spectra were recorded on a Jeol SX 102 spectrometer using FAB positive ionisation and glycerol as matrix.

***tert*-Butyl Glycinate.-** In a flask cooled to -40°, ammonia (100 mL) was condensed, then diluted with anhydrous ether (100 mL). To this solution, *tert*-butyl bromoacetate (50 g, 0.25 mol.) in ether (50 mL) was slowly added at -40° and the temperature was maintained for 2 hours, then allowed to warm to room temperature. After stirring overnight, the ammonium bromide was filtered off and the filtrate evaporated under reduced pressure to yield the title compound as an oil (29.5 g, 90%) . TLC on silica gel (AcOEt): Rf = 0.4. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 9H, tBu), 2.80 (s broad, 2H, NH_2), 3.45 (s, 2H, CH_2). This compound can be used without further purification or distilled (bp. 47°/0.7mm; lit.[4], bp. 30°/0.2mm.

***tert*-Butyl Glycinate Hydrochloride.-** Gaseous dry hydrogen chloride was slowly bubbled through a cooled (-10°) solution of crude *tert*-butyl glycinate in anhydrous ether. After 10 min, the precipitate was filtered off and the filtrate treated again with hydrogen chloride and filtered. This operation was repeated until complete precipitation. The hydrochloride of *tert*-butyl glycinate was isolated quantitatively as a white powder, mp. 142°, lit[11], mp. 137-140°. MS positive FAB : $M+H^+ = 131$.

***tert*-Butyl Sarcosinate.**- *tert*-Butyl sarcosinate, bp. 74-78°, lit.[12], bp. 76.5-78°/0.4mm, was obtained in 78% yield by the identical procedure using $MeNH_2$ in place of NH_3. TLC on silica gel (AcOEt/MeOH, 95/5 v/v): Rf = 0.28. ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H, *t*-Bu), 1.68 (s, 1H, NH), 2.48 (s, 3H, $N-CH_3$), 3.30 (s, 2H, CH_2). This compound was directly and quantitatively transformed to the *tert*-butyl sarcosinate hydrochloride, mp. 144° (MeOH/ether); (authentic sample from Novabiochem, Switzerland, mp. 145°). MS positive FAB : $M+H^+ = 145$.

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