the benzotropenylium cation (where the 1–6 interaction is, of course, well developed).

Perhaps more than anything, the results of this study highlight the complex interplay of perturbations which determine the electronic structure of the bridged annulenes. Similar conclusions have been drawn by other authors.[8,14]

Registry No.—1, 29534-58-5; 2, 2443-46-1.

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(7) Note that the inductive effect of the bridge group cannot affect the bond orders of **2** ($\pi_{i,kl} \equiv 0$ for alternant hydrocarbons). Even for **1** none of the properties examined in this study showed any obvious relationship to inductive perturbations by the bridge[8] (as calculated[5] via the quantities $\pi_{i,k}$ and $\pi_{i,kl}$).

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Efficient Preparation of N^{α}-Formylamino Acid *tert*-Butyl Esters

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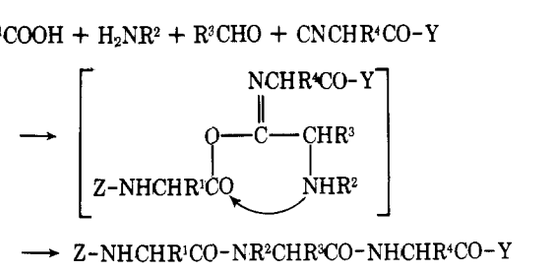
The formyl group has been a very useful amino-protecting group in peptide synthesis,[1] and could serve in combination with the selectively removable *tert*-butyl ester group in synthesizing suitably protected trifunctional amino acid derivatives. This study has been concerned with the development of an efficient procedure for preparing N^{α}-formylamino acid *tert*-butyl esters with minimal or no racemization. These compounds can be readily converted into isocyano acid *tert*-butyl esters required as one of the starting materials in four-component condensations (FCC). The FCC method of Ugi et al.[2] offers a unique and interesting new approach to peptide synthesis. In this reaction a carboxylic acid, an amine, and an aldehyde are combined with an isonitrile, such as an isocyano acid ester, to produce a tripeptide (Scheme I). Several known isocyano acid methyl (Y, OCH_3) and ethyl (Y, OC_2H_5) esters have been used in four-component condensations,[3] but *tert*-butyl isocyanoacetate[4–6] is the only known *tert*-butyl ester [Y, $C(CH_3)_3$] of an α-isocyano acid. These esters may be prepared by dehydration of intermediate N^{α}-formylamino acid esters.

Scheme I



Z = NH_2 protecting group
R^1, R^4 = amino acid side chain
R^2, R^3 = alkyl, aryl
Y = COOH protecting group

Known procedures for the preparation of N^{α}-formylamino acids proved to be unsatisfactory for producing their respective *tert*-butyl esters. The synthetic route to the preparation of N^{α}-formylglycine *tert*-butyl ester by treatment of *tert*-butyl chloroacetate with formamide[6] is not applicable to optically active amino acids without racemate resolution. Attempts at preparing *tert*-butyl esters of N^{α}-formylamino acids by the acid-catalyzed isobutylene procedure[7] provided the desired products, but only in very low yields. Standard N^{α}-formylation of amino acids or esters by formic acid and acetic anhydride[8] was incompatible with the *tert*-butyl ester group. However, the use of dicyclohexylcarbodiimide for the preparation of N^{α}-formylamino acid benzyl esters, reported by Thomas,[9] offered a route compatible with the *tert*-butyl protecting groups. We wish to describe a modified procedure for the efficient preparation of N^{α}-formylamino acid *tert*-butyl esters in high yields using formic anhydride[10] in pyridine.

Thus, dropwise addition of a preformed mixture consisting of formic acid (4 equiv) and dicyclohexylcarbodiimide (2 equiv) in chloroform at 0 °C to a solution of leucine *tert*-butyl ester in pyridine produced N^{α}-formylleucine *tert*-butyl ester (**2**) in 87% yield after purification by silica gel column chromatography, which removed a small amount of the side product 1,3-dicyclohexyl-1′,3′-diformylurea. The absence of racemized product was ascertained by converting **2** into N^{α}-formylleucine by treatment with trifluoroacetic acid and comparison of the product with an authentic sample[11] obtained by an independent procedure.[8] Other compounds prepared by our procedure are listed in Table IA.

The use of equivalent amounts or smaller excesses of reagents, i.e., 2 or 3 equiv of formic acid and 1 or 1.5 equiv of dicyclohexylcarbodiimide, resulted in considerably lower yields of **2** (28 or 57%, respectively). Attempts to prepare compound **2** by the isobutylene method[7] afforded the product in unacceptably low yields (17%).

The isocyano acid *tert*-butyl esters **5** and **6** were obtained from **1** and **2**, respectively, by dehydration with phosgene[3,13] followed by silica gel column chromatography in overall yields of 84 and 85% based on the starting amino acid *tert*-butyl esters.

Experimental Section

Amino acid *tert*-butyl esters were purchased from Bachem Inc., Marina Del Rey, Calif. Ester hydrochlorides were converted into free amines prior to use.[14] All optically active amino acids were of the L configuration.

***N*-Formylglycine *tert*-Butyl Ester (1).** A 2 M solution of formic acid in $CHCl_3$ (80 mL) was added dropwise with stirring and ice-bath cooling to a solution of dicyclohexylcarbodiimide (16.51 g, 80 mmol) in $CHCl_3$ (100 mL). The mixture was further stirred for 5 min, and then added with stirring over a period of 30 min into an ice-cold solution of glycine *tert*-butyl ester (5.25 g, 40 mmol) in pyridine (100

Table I

A. N^{α}-Formylamino Acid *tert*-Butyl Esters (For-AA-OBu^t)

Compd[a]	Formula[b]	Yield, %	R_f[c]	Bp, °C (mmHg)[d]	$[\alpha]^{25}_D$, deg, in EtOH
Gly (1)	$C_7H_{13}NO_3$	89	0.71	124–126 (0.5)	
Leu (2)	$C_{11}H_{21}NO_3$	87	0.79	143–144 (0.5)	−48.93 (*c* 2)
Pro (3)	$C_{10}H_{17}NO_3$	90	0.82	125.5–126.5 (0.6)	−109.79 (*c* 0.9)
Phe (4)	$C_{14}H_{19}NO_3$	88	0.83	171–172.5 (0.6)	15.97 (*c* 0.7)

B. 2-Isocyano Acid *tert*-Butyl Esters Derived from For-AA-OBu^t

Compd[a]	Parent amino acid	Formula[b]	Yield, %	R_f[c]	Bp, °C (mmHg)[d]	$[\alpha]^{25}_D$, deg, in EtOH
5	Gly	$C_7H_{11}NO_2$	94	0.90	91–93 (0.95)[e]	
6	Leu	$C_{11}H_{19}NO_2$	98	0.93	107 (0.45)[f]	−7.67 (*c* 1)

[a] NMR and IR spectral data agreed with the expected values. [b] Elemental analyses agreed with the calculated values within ±0.3%. [c] Solvent system for TLC (silica gel G) was $CHCl_3$–CH_3OH (96:4). [d] Boiling points were uncorrected. [e] Lit.[6] 87–89 °C (0.15 mm). [f] Compound 6 vaporized completely at this temperature.

mL). The mixture was then stirred for 4 h in an ice bath. Evaporation of the solvent was followed by addition of ether. The deposited dicyclohexylurea was removed by filtration and washed with ether. The combined filtrate was concentrated to an oil, which was purified by column chromatography on silica gel 60 (43 × 4.2 cm, 0.2–0.5 mm, E. Merck) using $CHCl_3$ followed by $CHCl_3$–CH_3OH (96:4) as eluents. Evaporation of the main peak fractions yielded 5.67 g of 1 as a colorless oil (89%). Several N^{α}-formylamino acid *tert*-butyl esters were prepared in this manner. The yields and physical constants of these compounds are summarized in Table IA.

A faster eluting side product was isolated by the above column chromatography and obtained as an oil (756 mg) which gradually crystallized. Recrystallization from ether–petroleum ether gave white needles. The compound was identified by NMR spectroscopy in $CDCl_3$ as 1,3-dicyclohexyl-1′,3′-diformylurea: mp 98.5–99.5 °C; R_f 0.94 (TLC, $CHCl_3$–CH_3OH, 96:4).

Anal. Calcd for $C_{15}H_{24}N_2O_3$ (280.4): C, 64.26; H, 8.63; N, 9.99. Found: C, 64.08; H, 8.68; N, 9.68.

***tert*-Butyl 2-Isocyanoacetate (5).** A solution of phosgene (990 mg, 10 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a vigorously stirred solution of 1 (1.59 g, 10 mmol) and triethylamine (3.4 mL, 24 mmol) in CH_2Cl_2 (5 mL) at 0 °C over a period of 30 min. The solution was stirred for an additional 30 min, filtered, and the filtrate concentrated in vacuo. Ether was added to the residue followed by filtration and concentration. The residue was purified by chromatography on a silica gel column (20 × 2.4 cm) with $CHCl_3$ as an eluent. The fractions containing 5 were combined and evaporated to yield a pale yellow oil (1.33 g, 94% yield). For physical constants see Table IB.

***tert*-Butyl 2-Isocyano-4-methylvalerate (6).** Prepared in 98% yield from 2 (215 mg, 1 mmol) as described above, but using *N*-methylmorpholine as a base and a reaction temperature of −30 °C.[3] The filtrate was concentrated in vacuo. Benzene was added to the residue followed by filtration and concentration. Chromatographic purification afforded 6 as a pale yellow oil, see Table IB.

Registry No.—1, 51354-15-5; 2, 61900-40-1; 3, 61930-75-4; 4, 61900-41-2; 5, 2769-72-4; 6, 61900-42-3; formic acid, 64-18-6; glycine *tert*-butyl ester, 6456-74-2; leucine *tert*-butyl ester, 21691-53-2; proline *tert*-butyl ester, 2812-46-6; phenylalanine *tert*-butyl ester, 16874-17-2; 1,3-dicyclohexyl-1′,3′-diformylurea, 61900-29-6.

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Alkylation of 2-Naphthol by Alcohols in the Presence of Base[1]

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1-Alkyl-2-naphthols and their derivatives are useful as antibacterial substances and antioxidants.[2] These compounds have been obtained by acylation of 2-naphthol and subsequent reduction of the carbonyl group,[3] as a by-product of the Williamson ether synthesis from alkyl halide and sodium naphthyl oxide,[4] by heating a mixture of 2-naphthol or 2,2′-dihydroxy-1,1′-dinaphthylmethane, an excess of sodium methoxide, and methanol,[5] by dehydrogenation of 1-methyl-2-oxo-2,3,4,6,7,8-hexahydronaphthalene or of 1-propyl-2-hydroxy-5,8-dihydronaphthalene,[6] and by reaction of 2-naphthol with formaldehyde and thiols ($C_nH_{2n+1}SH$) in ethanol in the presence of triethylamine.[7]

The authors have found a novel method to synthesize 1-alkyl-2-naphthols in good yield by a one-step reaction from alkali 2-naphthyl oxide and alcohol in the absence of catalyst.

Results and Discussion

Heating potassium 2-naphthyl oxide in primary alcohol gave 1-alkyl-2-naphthol. The yields and physical properties (boiling point and melting point) of the 1-alkyl-2-naphthols so obtained are listed in Table I. When potassium 2-naphthyl oxide was heated in pentyl alcohol at 200 °C for 5 h, 1-pentyl-2-naphthol was not obtained. Good yields were obtained, however, in 5 h at temperatures higher than 260 °C. In the present reaction, benzyl alcohol and primary aliphatic alcohols with more than three carbon atoms were effective.