Tetrahedron Letters No. 26, pp 2205 - 2208, 1976. Pergamon Press. Printed in Great Britain.

SYNTHETIC ROUTES TO α-AMINO ACIDS. C-ALKYLATIONS OF THE HIPPURIC ACID TRIANION AND THE ETHYL HIPPURATE DIANION

A. Paul Krapcho* and Edward A. Dundulis

Department of Chemistry, The University of Vermont
Burlington, Vermont 05401

(Received in USA 5 April 1976; received in UK for publication 17 May 1976)

As part of a continuing study dealing with the synthetic applications of α-anions of carboxylate salts (1), we wish to report successful C-alkylations of the trianion prepared from hippuric acid and the dianion derived from ethyl hippurate. The alkylated products can be readily hydrolyzed and these procedures constitute convenient two-step synthetic routes to α-amino acids.

Treatment of hippuric acid 1 with lithium diisopropylamide (LDA) in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) (3.3 equivs. of each per equiv. of acid) in a THF solution yields a red-colored solution of the trianion 2. Addition of CH_3I or $(CH_3)_2SO_4$ followed by

$\phi CONHCH_2CO_2H$ (1) $\qquad$ $\phi CONCHCO_2^{-3}\ 3Li^+$ (2) $\qquad$ $\phi CONHCHRCO_2H$ (3)

acidification produces 3 (R = CH_3) in isolated yields of 50-60%. Addition of ϕCH_2Br to the trianion 2 leads to 3 (R = ϕCH_2) in 40-50% yields. Attempts to alkylate 2 with $(CH_3)_2CHCH_2Br$ met with limited success since only 23% of product was recovered which contained 90% of 3 (R = $(CH_3)_2CHCH_2$) (nmr analysis of the crude reaction product). The formation of the trianion 2 is also supported by approximately 80% deuterium incorporation (D_2O quenching) at the α-position in the recovered hippuric acid (nmr analysis after water washing to remove the exchangeable amide and acid deuterons).

Attempts to generate 2 and subsequently alkylate it with CH_3I in the absence of TMEDA led only to recovery of 1 (85%). Trianion 2 was also formed by treatment of 1 with n-BuLi or t-BuLi in THF containing TMEDA. However, addition of CH_3I to the trianion prepared in this manner led

only to about 40% yield of 3 (R = CH_3), which was contaminated with 10% of unalkylated 1. The use of LDA-TMEDA to prepare the trianion 2 appears to be the method of choice.

The α-substituted hippuric acids 3 (R = CH_3, ϕCH_2, and $(CH_3)_2CHCH_2$) should be readily hydrolyzed to the α-amino acids glycine, phenylalanine, and leucine using procedures described below.

General Procedure. A solution of diisopropylamine (33 mmol) and TMEDA (33 mmol) in anhydrous THF (50 ml) was treated with n-butyllithium (33 mmol, 2.5 M in hexane) at -75° under a N_2 atmosphere and the mixture was stirred for 20 min. Hippuric acid (10 mmol) was added at -75°, and the mixture was heated at 50° for 1 hr. The red solution was then cooled to -75° and the alkylating agent (CH_3I, 13 mmol; ϕCH_2Br, 30 mmol) was added. In the case of CH_3I the mixture was allowed to warm to room temperature and stirring was continued overnight. The reaction mixture was quenched with ice, the layers were separated and the aq. phase was extracted with ether. The aq. phase was acidified with dil. HCl and the product extracted into ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. The crude product 3 (R = CH_3) was purified by column chromatography over silica gel. Pure 3 (R = CH_3) had a mp of 163-164°; lit. mp, 162.5-163.0° (D. T. Elmore and J. R. Ogle, J. Chem. Soc., 1141 (1958)). In the case of ϕCH_2Br the stirring was continued at -75° for 5 hr and then overnight at room temperature. The reaction mixture was quenched as above and acidification led to 3 (R = ϕCH_2), which was crystallized from ethyl acetate or ethanol; mp 183-184°; lit. mp 184.5-185.5° (A. R. Kidwai and G. M. Devasia, J. Org. Chem., 27, 4527 (1962)).

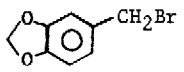
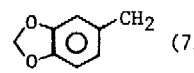
In the hope of improving the yields of the alkylated products, we next turned our attention to alkylations of ethyl hippurate. Treatment of ethyl hippurate 4 with LDA and TMEDA (2 equivs. of each per equiv. of ester) in THF produces the dianion 5. Addition of D_2O to the yellow suspen-

$\phi CONHCH_2CO_2Et$ (4) $\phi CONCHCO_2Et^{-2}\ 2Li^+$ (5) $\phi CONHCHRCO_2Et$ (6)

sion of 5 in THF leads to recovered 4 which shows a deuterium incorporation of 80% at the α-position (nmr analysis of the recovered ethyl hippurate after treatment with water to remove the amide deuteron). The results of C-alkylation of 5 with several alkyl and benzylic halides are tabulated in Table 1.

TABLE I

α-ALKYLATIONS OF THE DIANION 5

RX	PRODUCT 6 (% YIELD)[a]	mp, °C
CH_3I	R = CH_3 (48)[b]	72-73[e]
ϕCH_2Br	R = ϕCH_2 (61)[c]	94-95[f]
$(CH_3)_2CHI$	R = $(CH_3)_2CH$ (17)[d]	65-66[g]
	R =  (71)[d]	82-83[h]

[a]Isolated yields of pure compounds. Actual yields are higher.

[b]A 17% yield of 3 (R = CH_3) was also isolated.

[c]A 7% yield of 3 (R = ϕCH_2) was also isolated.

[d]No alkylated acids were isolated.

[e]Lit. mp 75-76°; I. W. Elliott, J. Org. Chem., 27, 3302 (1962).

[f]Lit. mp 95-95.5°; M. L. Bender and B. W. Turnquest, J. Amer. Chem. Soc., 77, 4271 (1955).

[g]Lit. mp 65-68°; S. W. Fox and H. Wax, J. Amer. Chem. Soc., 73, 2936 (1951).

[h]A satisfactory nmr spectrum was obtained. Analytical data; Calcd for $C_{19}H_{19}NO_5$, C, 66.85; H, 5.61; Found, C, 66.86; H, 5.72.

It can be seen from the tabulated data that good yields of 6 can be obtained when CH_3I, ϕCH_2Br, and piperonyl bromide are used as the alkylating agents. Even isopropyl iodide leads to 6 (R = $(CH_3)_2CH$) although it proceeds in a poor yield. Low yields of the alkylated acids were also isolated from the alkylations of dianion 5 with CH_3I and ϕCH_2Br, along with the expected esters 6. The pathway for competitive formation of these acids is unclear, but it is possible that partial hydrolysis might have occurred under the acidic workup conditions.

General Procedure. A solution of diisopropylamine (20 mmol) and TMEDA (20 mmol) in THF (50 ml) at -75° was treated with n-BuLi (20 mmol, 2.5 M in hexane) and then stirred for 20 min. Ethyl hippurate (10 mmol) dissolved in THF (20 ml) was added dropwise so that the temperature remained below -70°. The thick yellow suspension was stirred for an additional hr at -75°. The alkylating agent (10 mmol) was then added, and the reaction was stirred for 1 hr at -75°. The mixture was allowed to warm to 0°, poured over ice, and the layers were separated. The THF layer was washed with water, and the combined aqueous fractions were extracted with ether. The combined organic

fractions were washed with cold 2N HCl, and the acidic wash was extracted with ether. The organic extracts were dried over $MgSO_4$ and concentrated. The crude esters were crystallized from benzene/pentane. The combined aqueous portions from the original quenching were acidified and extracted with ethyl acetate. The extracts were dried over $MgSO_4$ and concentrated. The crude acids were crystallized from ethyl acetate or ethanol.

Hydrolysis of 6 (R = CH_3 or ϕCH_2) with 48% HBr (3) produces alanine and phenylalanine in 80 and 85% yields, respectively. Hydrolysis of 6 (Entry 4, Table I) following the procedure described for the N-acetamido analog (4) leads to DL-DOPA (5) in a 60% yield. In a similar fashion the acids 3 could also be readily hydrolyzed to the corresponding α-amino acids.

Further extensions of these reactions are currently under active investigation.

Acknowledgement: The authors would like to acknowledge the financial support of an Institutional Grant from a Public Health Service Grant to the University of Vermont and a Fellowship from The Humphrey Chemical Company, North Haven, Connecticut, 06473.

REFERENCES

1. A. P. Krapcho and D. S. Kashdan, Tetrahedron Letters, 707 (1975), and references cited therein.

2. (a) M. D. Rausch and A. J. Sarnelli, "Polamine-Chelated Alkali Metal Compounds," Advances in Chemistry Series, Number 130, American Chemical Society Publication, 248 (1974).
   (b) M. D. Rausch and D. J. Ciappenelli, J. Organometal. Chem., 10, 127 (1967).

3. C. E. Redemann and M. S. Dunn, J. Biol. Chem., 130, 341 (1939).

4. S. Yamada, M. Yamamoto, and I. Chibata, J. Org. Chem., 40, 3360 (1975).

5. F. W. Bollinger and M. E. Jaffe, Chemtech., 5, 589 (1975), for a review of the use of DOPA in treatment of Parkinson's disease.