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NEW SYNTHESIS OF DL-α- AMINOACIDS FROM t-BUTYL N(DIPHENYLMETHYLENE) OXAMATE

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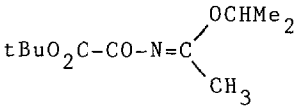
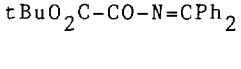
The condensation of phosphorus ylids with t-butyl N(diphenylmethylene) oxamate gives 2-aza 1,3-dienes ; subsequent reduction with sodium cyanoborohydride provides protected α-aminoacids.

In a previous paper (1), we have shown t-butyl alkylidene oxamate 1 to be good precursor of protected α-dehydro α-aminoacids. In this preliminary account, we report a new route to α-aminoacids using t-butyl N(diphenylmethylene) oxamate 2 as starting material.



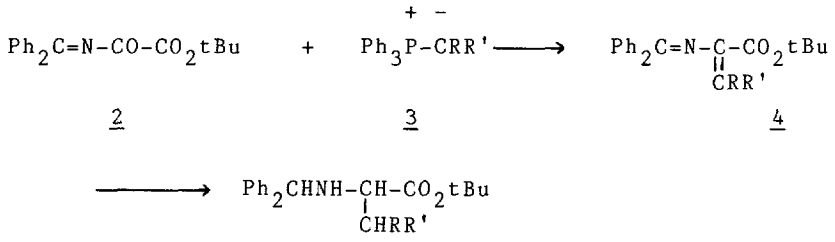
1



2

This compound 2 is readily available (86% yield) from crude t-butoxalyl chloride (2) and commercial diphenylketimine.

The oxamate 2 , like 1, is a very reactive electrophilic compound, which reacts with non-stabilized (3a, 3b) , semi-stabilized (3c) and stabilized (3d and 3e) ylids to give the corresponding azadienes 4.



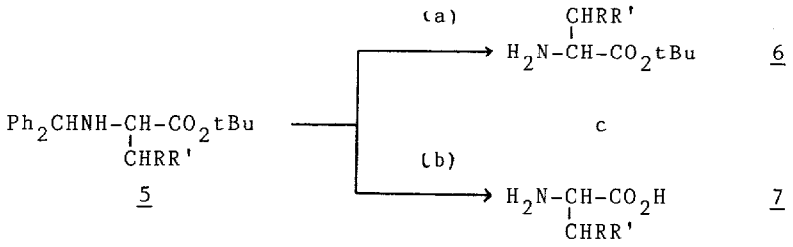
2 3 4

5

3, 4, 5 : a R = C_3H_7, R' = H ; b R, R' = cyclobutyl ; c R = Ph, R' = H ; d R = MeO_2C-, R' = H ; e R = CH_3CO-, R' = H ; 5e : R = $CH_3CH(OH)$, R' = H.

Hydrolysis of 4 (1 equ.of aqueous HBr 0.5 M) results only in the formation of α-ketoester. Selective reduction of the imine function by sodium cyanoborohydride, under acidic conditions does not occur but treatment of 4 with a large excess of reagent provides α-aminoesters 5 in good yields . In these conditions, we observed reduction of the keto group during transformation of 4e to 5e .

The compounds 5 can lead to the α-aminoesters 6 by hydrogenolysis (a) in the presence of formic acid (1.5 equ.). Hydrogenolysis of 5 in acetic acid (large excess) at refluxing temperature (b) gives directly the free α-aminoacids 7 . The use of trifluoroacetic acid allows transformation of 6 to 7 in quantitative yields.



A typical procedure is as follows :
1 equ. of t-butoxalylchloride was added to a stirred solution of 1 equ. of diphenylketimine and 1 equ. of triethylamine in dry ether to give 2 (86% yield, m.p. 72-73 °C). 1 equ. of 2 was added to a stirred solution of 1 equ. of ylid 3 in dry toluene. Upon completion of the reaction (10 min r.t for 3a, 3b, 4 h under reflux for 3c and 12 h under reflux for 3d and 3e) the solvent was evaporated and the azadiene separated from triphenylphosphine oxide with hexane and purified by recristallization. Transformation of 4 to 5 was obtained by adding a large excess (4 moles) of sodium cyanoborohydride to a solution of 4 and 1.5 equ. of acetic acid in dry THF. After 24 h under reflux the compound 5 was isolated and used crude . Hydrogenolysis was run in methanol under hydrogen in the presence of 1.5 equ. of formic acid and an equal weight of 10% Pd/C to give 6.

Table - Compounds 4 , 5 , 6, 7 prepared (3)

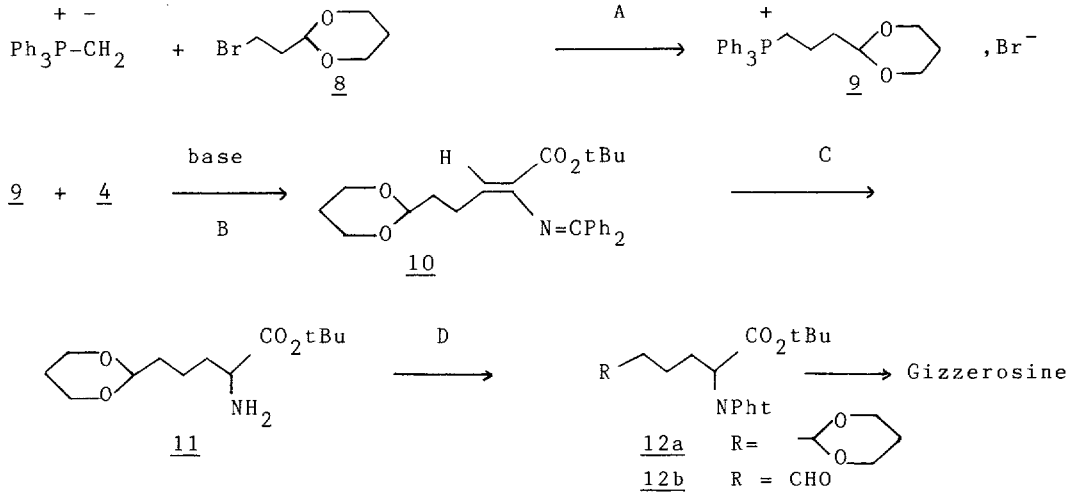
			4		5		6	7	
	R	R'	yield (%)	mp (°C)	yield (%)	mp (°C)	yield (b) (%)	yield (%)	mp (lit)[4] (°C)
a	$n\text{-}C_3H_7$	H	82	75-76	98	oil[a]	57	90	300 (297-300)
b	cyclobutyl		70	oil[a]	96	oil[a]	59	80	240 dec[5]
c	C_6H_5	H	60	85-87	95	94(MeOH)	60	89	265 (266-267)
d	MeO_2C	H	70	84-86	95	oil[a]	71	85	334 (338-339)
e	CH_3CO[c]	H	54	85-87	94	89-94 (hexane)	70	80	204-210 (212)

(a) - crude product directly utilized

(b) - compounds 6 were obtained by chromatography on alumine oxide with toluene/ ethyl acetate as eluent.

(c) - for compounds 5e and 6e, R = $CH_3CH(OH)$-

This new route to α-aminoacids is very general , for instance, this procedure may be adapted for the preparation of the α-aminoester 11,a direct precursor of (±) Gizzerosine (6).



REACTION CONDITIONS

A . 8 was added at room temperature to a stirred solution of ylid in dry toluene. After 5h under reflux, 9 was filtered , dissolved in chloroform and precipitated by adding ethyl acetate (87% yield,mp.210-220°C).

B . To a suspension of 9 in dry toluene was added 1.1 equ. of tBuOK, then 1 equ. of 4 at 0°C. After 15 min at room temperature the solvent was evaporated and 10 was separated from triphenylphosphine oxide by treatment with hexane(oil, 77% yield , ^1H 1.35 (s, tBu) ,3.50 to 4.30 (m, 3 CH_2),4.50 (t, J=5 Hz, CHO), 6.00 (t, J= 7 Hz, =CH) .

C . To a solution of 10 in dry methanol was added 1.5 equ. of formic acid and an equal weight of 10% Pd/C . After 24h at 50°C ,the suspension was filtered and evaporated to give 11 (oil obtained by column chromatography on alumina with toluene/ ethyl acetate as eluent , 60% yield, ^1H 1.50 (s, tBu), 3.30 (t, J= 7 Hz, C<u>H</u>NH_2),3.55 to 4.15 (m, 3 CH_2),4.55 (t, J= 5 Hz, CHO)).

D . i)(5mmol of 11 / 5 mmol of phtalic anhydride/ 0.1 mL Et_3N) ;12a (white solid, 90% yield, m.p.$_{tBuOMe}$=80°C, ^1H 1.45(s, tBu),3.55 to 4.20 (m, 3 CH_2), 4.00 (t, J=6 Hz, OCHO), 4.30 (t, J= 7.5 Hz, CHN),7.85 (m, Pht).ii) (5 mmol of 12a in 2mL of formic acid / 1h/ 80°C). 12b (unstable oil,95% yield, ^1H 1.28 (s, tBu), 4.92 (t, J= 7.5 Hz, CHN), 7.85 (m, Pht), 9.80 (broad, CHO).

REFERENCES

1 - J.P. BAZUREAU, M. LE CORRE, Tetrahedron Lett., 1988, 29, 1919

2 - J.S. NIMITZ, H.S. MOSHER, J.Org.Chem., 1981, 46, 211

3 - Selected ^1H NMR data ($CDCl_3$, δ ppm, at 60 MHz):
4a: 1.30 (s, tBu), 5.83 (t, =CH, J = 7.5 Hz);
4b: 1.38 (s, tBu), 7.32 (m, Ph); 4c: 1.27 (s, tBu), 6.76 (s, =CH);
4d: 1.40 (s, tBu), 3.53 (s, OCH_3), 5.80 (s, =CH);
4e: 1.33 (s, tBu), 2.10 (s, CH_3), 6.05 (s, =CH);
5a: 1.50 (s, tBu), 3.08 (t, CHCO-), 4.85 (s, CHNH);
5b: 1.48 (s, tBu), 3.05 (d, J=6Hz, C<u>H</u>NH), 4.80 (s, C<u>H</u>Ph_2);
5c: 1.40 (s, tBu), 3.35 (t, J=6Hz, C<u>H</u>CH_2), 4.82 (s, C<u>H</u>NH);
5d: 1.50 (s, tBu), 3.48 (t, J=6Hz, C<u>H</u>CH_2), 3.68 (s, OMe), 5.00 (s, C<u>H</u>NH)
5e: 1.15 (d, J=6Hz, CH_3), 1.50 (s, tBu), 4.80 (s, C<u>H</u>NH);
6a: 1.48 (s, tBu), 3.30 (t, J=6Hz, C<u>H</u>NH_2); 6b: 1.50 (s, tBu), 2.05(m,C<u>H</u>$_2$-);
6c: 1.45 (s, tBu), 7.35 (m, Ph); 6d: 1.48 (s, tBu), 3.70 (s, OMe);
6e: 1.20 (d, J=6Hz, CH_3), 1.50 (s, tBu);

4 - Dictionary Of Organic Compounds, Chapman and Hall, Publ.

5 - J.W. ANDERSON, L. FOWDEN, Biochem. J., 1970, 119, 691,no data given.

6 - K. MORI, T. SUGAI, Y. MAEDA, T. OKAZAKI, T. NOGUCHI, H. NAITO, Tetrahedron, 1985, 41, 5307

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