NOVEL CYCLIZATION OF ETHYL 2-BROMOPYRUVATE WITH DIALKYLTHIOAMIDES OF N-PROTECTED AMINO ACIDS: ONE POT SYNTHESIS OF 1,2,3,5-TETRASUBSTITUTED PYRROLES

Tarek S. Mansour* and Gilles Sauvé
Université du Québec, Institut Armand-Frappier, Biochemical Products Division, 531 Boulevard des Prairies, Laval, Québec, Canada H7V 1B7

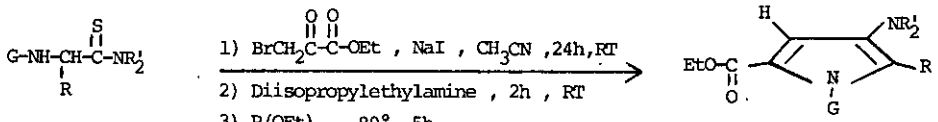
Abstract—Reaction of ethyl 2-bromopyruvate (1) with various N-t-Boc, N-ethoxycarbonyl or N-acetyl phenylalanine or methionine dialkylthioamides under sulfur extrusion conditions gave 1,2,3,5-tetrasubstituted pyrroles in good yields.

2-Halopyruvate esters are potent alkylators that have been widely used in the synthesis of heterocycles containing nitrogen,[1] sulfur or oxygen groups.[2] Of particular interest, is the condensation of primary thioamides with ethyl 2-bromopyruvate (1), known as the Hantzsch reaction,[3] to form the thiazole ring which is an important constituent of various antibiotics,[4] pharmacologically active peptides,[5] as well as the newly isolated series of cyclic cytotoxic peptides.[6] Recent procedures describing improvements on the Hantzsch reaction have resulted in excellent control over racemization,[7] frequently noted as a limitation of the reaction with chiral starting material. Here, we report the novel reaction of dialkylthioamides of N-protected amino acids with (1).

Thioamides (2) are efficiently prepared by thionation of the corresponding amides with 2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (PTPS) in anhydrous tetrahydrofuran at 20°C in excellent yields.[8] Thioamide (2d) was prepared from (2a) by removal of the t-Boc group with 98% formic acid followed by acylation. Under conditions previously implemented by Eschenmoser et al for the synthesis of enolizable 1,3-dicarbonyl compounds,[9] the reaction of 1-(thio-t-Boc-α-aminophenylalanyl)-azacyclopentane (2a) with (1) in acetonitrile[10] containing one equivalent of anhydrous sodium iodide, followed by deprotonation of the intermediate thioimmonium salt with Huning's base and sulfur extrusion with triethylphosphite at 80°C, resulted in the formation of 1-t-Boc-2-benzyl-3-(1-azacyclopentane)-5-carboethoxypyrrole (3a) in 78% yield as outlined in Scheme 1. The expected products from the sulfur contraction method are the enaminoketoester or its hydrolysis product. These products were not isolated but reacted further to give pyrroles (3). Similarly, the morpholino ethoxycarbonyl derivative (2c) gave (3c) in somewhat lower yield (30%) together

with unreacted starting material. The lower yield of (3c) may be due to the reversible alkylation of thioamides.[10] Other amino acids such as the methionine derivative (2b) reacted in a similar fashion to afford pyrrole (3b) in 41% yield without apparent serious complications from the thioether group. Replacement of the carbamate functionality by acetyl as in (2d) resulted in smooth cyclization giving (3d) in good yield.

Scheme 1



(2) a ; G = t-Boc , R = CH_2Ph , $R'_2 = (CH_2)_4$

b ; G = t-Boc , R = $CH_2CH_2CH_3$, $R'_2 = (CH_2)_4$

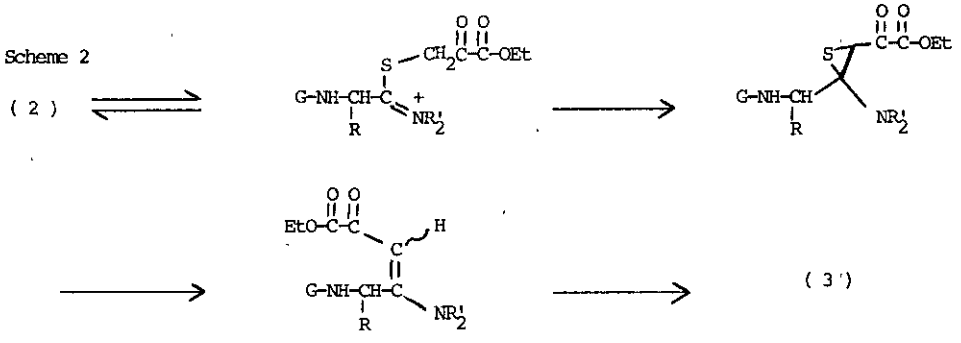
c ; G = EtO_2C , R = CH_2Ph , $R'_2 = (CH_2)_2O(CH_2)_2$

d ; G = Ac , R = CH_2Ph , $R'_2 = (CH_2)_4$ (3)

Spectroscopic properties of (3) are summerized in Table 1. The carbon - 13 nmr spectra show a methine group at 110-113 ppm with a coupling constant J_{13C-1H} of 173 Hz and a single proton at δ 6.5 - 6.9 ppm appear in the proton nmr spectra. These features are quite characteristic of 4 - unsubstituted pyrroles.[11]

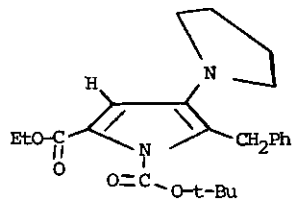
Although much remains to be done to establish the mechanism of these transformations, it seems reasonable to assume that the enaminoketoester is formed with E configuration, either after sulfur extrusion or through equilibrations, allowing the nitrogen of the carbamate or amide to attack the reactive carbonyl group. Proton shifts followed by dehydration would give pyrroles (3) as shown in scheme 2.

Scheme 2



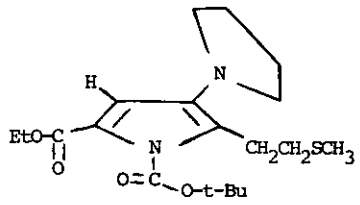
The above reaction introduces a simple and efficient entry to polysubstituted pyrroles, that can further be functionalized, from accessible starting metarial.

TABLE 1. Spectroscopy Properties of Pyrroles (3).



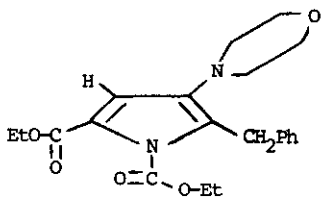
(3a) 56(78)[12]

^{1}H nmr CD_3OD δ 7.21 (d,J=7.3.2H),7.15(d,J=6.9,1H),7.01(d, J=6.9,2H),6.75 (s,1H),4.25(q,J=7.2,2H),4.23(s,2H),3.01(m, 4H),1.86(m,4H),1.32(t=7.1,3H),1.24(s,9H).
^{13}C nmr δ 160.0(s),149.0(s),139.3(s), 136.1(s),127.9(d), 127.7(d),125.8(s),125.6(d),121.9(s),110.5(d,J=173.2),83.9 (s),60.0(t),52.8(t),30.3(t),26.7(q),24.3(t),14.1(q).
υ 2980,1751,1716,765. Ms CI/NH_3 m/z 399($M+H^+$,59.6),398 (M^+,12.7),299(M^+-99,100).
$C_{23}H_{30}O_4N_2+H^+$ calcd 399.22829; found 399.22838.



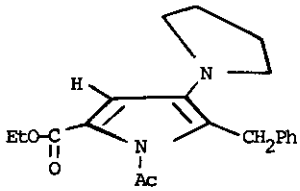
(3b) 30(41)[12]

^{1}H nmr $CDCl_3$ δ 6.57(s,1H),4.21(q,J=7.2,2H),3.00(m,6H),2.68 (m,2H),2.11(s,3H),1.84(m,4H),1.53(s,9H),1.28(t,J=7.2,3H).
^{13}C nmr δ 160.2(s),149.3(s),135.5(s),126.5(s),121.8(s),111.0 (d,J=173.3),84.4(s),60.1(s),52.6(s),33.4(t),27.2(q),25.7(t), 24.5(t),15.0(q),14.2(q).
υ 2978,1751,1716. Ms CI/NH_3 m/z 383 ($M+H^+$,100),283(M^+-99,79).
$C_{19}H_{30}N_2O_4S + H^+$ calcd 383.20056; found 383.20045



(3c) 15(30)[12]

^{1}H nmr $CDCl_3$ δ 7.19(m,3H),7.05(d,J=8.1,2H),6.88(s,1H),4.25(q, J=7.1,2H),4.18(s,2H),4.06(q,J=7.2,2H),3.73(m,4H),2.78(m,4H), 1.32(t,J=7.1,3H),1.07(t,J=7.1,3H).
^{13}C nmr δ 160.2(s),151.0(s),138.6(s),137.8(s),131.0(s),128.2 (s),128.1(d),127.9(d),126.1(d),122.7(s),112.6(d,J=173.7),67.1 (t),64.3(t),60.6(t),53.8(t),29.9(t),14.2(q),13.4(q).
υ 2965,1762,1709. Ms CI/NH_3 m/z 387($M+H^+$,100) 386(M^+,5)
$C_{21}H_{26}N_2O_5 + H^+$ calcd 387.19205;found 387.19200.



(3d) 40(70)[12]

^{1}H nmr $CDCl_3$ δ 7.31(m,1H),7.24(d,J=6.0,2H),7.02(d,J=6.6,2H), 6.78(s,1H),4.25(d,J=7.1,2H),4.17(s,2H),3.08(m,4H),2.03(s,3H), 1.88(m,4H),1.32(t,J=7.1,3H).
^{13}C nmr δ 174.1(s),160.4(s),139.2(s),136.9(s),128.4(d),128.2(d),127.4(s),126.1(d),120.7(s),111.3(d.J=173.5),60.5(t),52.9(t) 30.5(t),27.8(q),24.6(t),14.2(q). υ 2978,1742,1701,1654,756.
Ms CI/NH_3 m/z 341 ($M+H^+$,100).
$C_{20}H_{24}N_2O_3 + H^+$ calcd 341.18664; found 341.18652.

ACKNOWLEDGEMENTS

Financial support from both NSERC Canada for the industrial chair attributed to Professor B. Belleau and IAF Biochemicals is gratefully acknowledged.

REFERENCES

1. J.S.Duceppe and J.Gauthier, J. Heterocyclic Chem. , 1985 , 22 , 305 ; W.R.Mallory and R. W.Morrison Jr. , J. Org. Chem. , 1980 , 45 , 3919.
2. K.Ogawa, T.Terada, T.Yamazaki, S.Yamuda, T.Honna, S.ohter, and M.Okamoto, J. Chem. Soc. Perkin Trans. 1 , 1985 , 2417 ; P.Molina, A.Arques, and A.Fera, Synthesis , 1982 , 645 ; R.L.Titus and C.F.Titus, J. Heterocyclic Chem. , 1973 , 10 , 679 .
3. B.M.Dean, M.P.V.Mijovic, and J.Walter, J. Chem. Soc. , 1961 , 3394.
4. H.Kasai, H.Naganawa, T.Takita, and H.Umezawa, J. Antibiotics , 1978 , 31 , 1316.
5. R.Kazlaukas, R.O.Lidgard, R.J.Wells, and W.Vetter, Tetrahedron Lett. , 1977 , 3183.
6. J.M.Wasylyk, J.E.Biskupiak, C.E.Costello, and C.M.Ireland, J. Org. Chem. , 1983 , 48 , 445 and references cited therein ; G.R.Pettit, Y.Kamano, P.Brown, D.Gust, M.Inoue, and C.L.Herald , J. Am. Chem. Soc. , 1982 , 104 , 905.
7. R.Houssin, M.Lohez, J.L.Bernier, and J.P.Hénichart, J. Org. Chem. , 1985 , 50 , 2787 ; U.Schmidt, P.Gleich, H.Griesser, and R.Utz, Synthesis , 1986 , 992.
8. G.Lajoie, F.Lépine, L.Maziak, and B.Belleau, Tetrahedron Lett. , 1983 , 3815.
9. M.Roth, P.Dubs, E.Gotschi, and A.Eschenmoser, Helv. Chim. Acta , 1971 , 54 , 710.
10. R.E.Ireland and F.R.Brown, J. Org. Chem. , 1980 , 45 , 1868.
11. E.Pretschi, T.Clerc, J.Siebel, and W.Simon ' Tables of Spectral Data for Structure Determination of Organic Compounds , ' Springer-Verlag , Berlin , 1983.
12. Yields in paratheses are based on recovery of starting material . Pyrroles (3a-d) are oils.

Received, 7th September, 1987