ACETYLATION WITH ACETIC-1-^{13}-C PIVALIC ANHYDRIDE

Walter J. Horton, Steven P. Adams, and Mary W. Niermeyer
Isotopes Laboratory, Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, USA.
Received September 13, 1976
Revised October 27, 1977

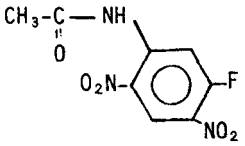
SUMMARY

In situ formation of acetic-1-^{13}-C pivalic anhydride constitutes a convenient and economical means of preparing C-13 containing acetanilides in excellent yield. Similarly, in situ formation of pivalic anhydride yields pivanilides. An elegant synthesis of p-acetylaminobenzaldehyde from p-nitrobenzaldehyde via the acetal is described.

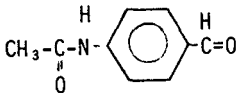
Key Words: ^{13}C acetylation, acetic pivalic anhydride, p-acetylaminobenzaldehyde, pivanilides

DISCUSSION

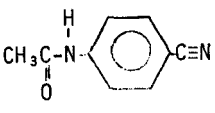
In an investigation of antigen-antibody interaction by means of C-13 nuclear magnetic resonance, the haptens 1, 2 and 3 were prepared and the first two were attached to several proteins for injection into rabbits. In each case acetic anhydride was used in the acetylation. We now report a more efficient and convenient method for the introduction of acetyl-1-^{13}C onto the anilines corresponding to 1, 2 and 3 and also several simple substituted anilines.



1



2



3

We have prepared acetic pivalic anhydride (1) in situ from pivaloyl chloride and anhydrous sodium acetate in refluxing acetonitrile. The aniline was then added without isolation of the reagent.

$$(CH_3)_3C\text{-}\overset{\overset{O}{\|}}{C}\text{-}Cl + Na^+ \bar{O}\text{-}\overset{\overset{O}{\|}}{C}OCH_3 \longrightarrow (CH_3)_3C\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3$$

As anticipated, the steric bluk of the pivaloyl group directed the attack to the acetyl side of the reagent. The results are shown in Table I.

Table I. Acetylation of $NH_2C_6H_4R$ using acetic pivalic anhydride

R	Yield %	M.P. °C	Reported M.P. °C
H	83	108-113	113-114 (2)
p-Cl	97	177-180	178.4 (2)
p-Br	99	163.5-168	168
o-Br	48	92-100	99 (2)
p-CH(OCH$_2$)$_2$	73[a]	93.5-110	--
p-CN	76[b]	198-202	202-203 (3)
p-CO_2H	59	246-253° dec	250° dec (2)
m-CO_2H	57[b]	244-250°	248° dec (2)
o-CO_2H	56[b]	179-184.5°	185° (2)

(a) Yield over two steps- a 20% excess of acetylating agent was used.

(b) Yield with ^{13}C labeled reagent.

The method, in addition to the economical use of the C-13 containing material, uses commerically available anhydrous sodium acetate-1-^{13}C, thus avoiding the preparation or purchase of a more expensive acetylating reagent.

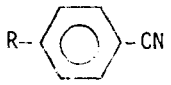
2,4-Dinitro-5-fluoroaniline failed to react under the conditions which gave the acetanilides in Table I. If, however, the filtered solution of

acetic pivalic anhydride was evaporated and the residual oil was combined with the aniline and catalyzed by sulfuric acid, 1 was obtained in 72% yield.

The acetylation of 2,4-dinitro-5-fluoroaniline using two moles of acetic anhydride gave 1 in 90% yield. With an equimolar amount of acetic anhydride the yield was 79%. Difficulty was found when other acetylation reagents were used probably due to the lower basicity of the amine, the activity of the fluoro group and the bulk of the ortho substituent. The low yield in the acetylation of o-bromoaniline (Table I) indicates the influence of a large ortho group.

The acid-sensitive p-aminobenzaldhyde ethylene glycol acetal (Table I) required modification of the general acetylation procedure. Solid sodium carbonate was added to the reagent after removal of acetonitrile. The freshly prepared amino acetal dissolved in acetonitrile was then added and treated thereafter as in the general procedure (see Experimental).

The pivanilides in Table II were prepared using sodium pivalate and pivaloyl chloride in acetonitrile to prepare pivalic anhydride. The aniline was then added without isolation of the reagent.



4 R, NO_2 5 R, NH_2

The reaction of p-bromonitrobenzene with copper(I) cyanide to give 4 in 76% yield (4) indicates potential for a ^{13}C label in the cyano group. Hydrogenation of 4 over platinum gave 5 in 96% yield and acetylation of 5 with acetic-1-^{13}C pivalic anhydride gave labeled 3 in 76% yield.

Table II. Pivaloylation of $NH_2C_6H_4R$ using pivalic anhydride

R	Yield %	M.P. ^{o}C	Reported M.P. ^{o}C
H	87	131-135	132 (5)
p-Cl	93.5	151-153	148-149 (6)
p-Br	79	154-158	156-157 (7)
o-Br	54.7	54-58	--[a]

(a) Calcd. for $C_{11}H_{14}NOBr$: C, 51.58, H, 5.51, N, 5.47 Found: C, 51.76, H, 5.58, N, 5.36; m.p. 60-61.5^{o} from aqueous ethanol.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. PMR were obtained on an EM-390 spectrometer. CMR spectra were obtained on a Varian XL-100. Good quality acetonitrile was redistilled from phosphorus pentoxide and stored over 3A molecular sieve.

General Acetylation Procedure (See Table I). A suspension of 0.45 g. (5.5 mmol) of finely crystalline anhydrous sodium acetate in 20 ml of acetonitrile was combined with 0.67 ml (5.5 mmol) of pivaloyl chloride and refluxed on the steam bath with stirring for 1 hr. The mixture was cooled, 5.0 mmol of the aniline was added and refluxing continued for 3 hr. The solvent was then distilled (aspirator) and the solid residue was stirred and warmed on the steam bath for 15 min with 20 ml of 4% aqueous sodium bicarbonate, chilled, filtered and washed with ice cold water. The acetanilides were identical to authentic compounds by mixed melting point and by PMR.

Pivaloylation (See Table II). The procedure was identical to the above with replacement of the sodium acetate by 0.68 g. (5.5 mmol) of powdered anhydrous sodium pivalate.

2,4-Dinitro-5-fluoroacetanilide (1). 2,4-Dinitro-5-fluoroaniline (Pierce Chemical Co.; 0.20 g, 1 mmol) was heated on the steam bath for 3 hr with 0.2 ml (2.12 mmol) of acetic anhydride containing sulfuric acid (1 drop per 10 ml), cooled, stirred with water and filtered to obtain 0.22 g. (90%) of product m.p. 111-119° (lit. (8) 119°).

N-(2,4-dinitro-5-fluorophenyl) acetamide-1-^{13}C. The general acetylation procedure above with 0.67 ml (5.5 mmol) of freshly distilled pivaloyl chloride and 0.45 g. (5.5 mmol) of anhydrous sodium acetate-1-^{13}C (90% C-13) with refluxing for 3 hr was used to give the mixed acid anhydride. The sodium chloride was filtered off and the solvent removed *in vacuo*. The residual oil was combined with 1.0 g. (5 mmol) of 2,4-dinitro-5-fluoroaniline, 0.5 ml of anhydrous acetonitrile and 2 microdrops of concentrated sulfuric acid and warmed 3 hr with stirring on the steam bath. The solid product with 10 ml of water was neutralized with 4% aqueous sodium bicarbonate, chilled, filtered and washed with water. After drying, the solid was crystalized from benzene-hexane to

yield 0.87 g. (3.58 mmol; 72%) m.p. 102-113°.

A 12.0 mg. sample of the compound was dissolved in 1.5 ml of acetone-d_6, 2 drops of dioxane were added for internal reference and the CMR spectrum was acquired for a period sufficient to observe the signal resulting from the enriched carbon. The chemical shift was identical to that of an unenriched sample (170.2 ppm from TMS).

p-Nitrobenzaldehyde Ethylene Glycol Acetal. p-Nitrobenzaldehyde (6.77 g; 0.045 mol) in 600 ml of toluene with 0.52 g. of p-toluenesulfonic acid monohydrate and 113 ml of ethylene glycol was refluxed for 9 hr using a Dean-Stark trap. Distillation then removed 400 ml of toluene-ethylene glycol and the chilled solution was treated with excess saturated sodium bicarbonate and water, the layers were separated, the toluene washed repeatedly with water and removed in vacuo. The residual oil deposited 7.45 g. (0.038 mol; 85%) of practically colorless crystals; m.p. 86-93° from methanol-water (lit. (9, 10) 90.5°, 89-91°).

p-Aminobenzaldehyde Ethylene Glycol Acetal. A suspension of 3.90 g. (0.02 mol) of the above in 60 ml of ethanol with 0.4 g. of platinum oxide was shaken under hydrogen at slightly above atmospheric pressure until the hydrogenation rate dropped to 3-8 ml per min. Removal of the catalyst and solvent gave a pale yellow oil which could be acetylated directly. In one experiment the oil crystallized on standing overnight, m.p. 50-71° (lit. (10) 75-79°).

p-Acetylaminobenzaldehyde Ethylene Glycol Acetal. The above liquid amine in 60 ml of benzene with 8.3 ml of triethylamine and 3.76 ml (0.04 mol) of acetic anhydride was refluxed for 2 hr. The solvents were removed in vacuo, water was added and the flask chilled. The colorless crystals weighed 3.45 g. (0.0167 mol; 83.5% based on the nitro acetal), m.p. 98-114°. From benzene-hexane, purified material melted at 116-118°. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75, H, 6.32, N, 6.76 Found: C, 64.06, H, 6.50, N, 6.69.

p-Acetylaminobenzaldehyde. The crude acetal above was heated on the steam bath with 60 ml of 50% aqueous acetic acid for 30 min. The solvent was then removed in vacuo and traces of acetic acid were swept out by addition and distillation of 10 ml of water. The residue solidified on cooling, 2.4 g. (0.015

mol; 90%) m.p. 152-156.5° (lit. 153°). (2)

p-Benzamidobenzaldehyde. The amine acetal with benzoyl chloride and sodium hydroxide gave p-benzamidobenzaldehyde ethylene glycol acetal (87%) m.p. 112-135°. From aqueous methanol it melted at 152.5-153.5°. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36, H, 5.61, N, 5.20. Found C, 71.04, H, 5.45, N, 5.38. Cleavage of the acetal gave the aldehyde (97%) m.p. 135-155°. Crystallization from benzene-hexane gave a sample m.p. 150.5-151°. Calcd. for $C_{14}H_{11}NO_2$: C, 74.64, H, 4.93, N, 6.22. Found: C, 74.31, H, 4.85, N, 6.20.

p-Acetyl-1-^{13}C-aminobenzaldehyde (2). Acetic pivalic anhydride was prepared from 0.49 g (6. mmol) of powdered anhydrous sodium acetate-1-^{13}C and 0.74 ml (6 mmol) of pivaloyl chloride as described in the general procedure above. The solvent was then removed in vacuo and 1.06 g. of anhydrous sodium carbonate was added. Five millimoles (0.98 g.) of p-nitrobenzaldehyde ethylene glycol acetal was reduced over platinum oxide as described above and the residual oil evaporated twice with 10 ml of absolute ethanol and twice with 10 ml of anhydrous benzene to remove water and ethanol. The oil was transferred to the acetic pivalic anhydride above with three 10 ml portions of acetonitrile and refluxed for 3 hr. The solvent was evaporated in vacuo, the residue was digested on the steam bath for 15 min with 20 ml of 4% aqueous sodium bicarbonate, chilled, filtered and washed with ice water. The light yellow solid weighed 0.81 g. m.p. 93.5-110° From benzene-hexane, 0.55 g. (2.66 mmol; 53%) m.p. 113.5-116.5° was obtained. Cleavage of 0.52 g. (2.5 mmole) of this acetal as described above gave 0.36 g. (2.21 mmol; 88%) m.p. 153-156.5°. The CMR of a 10 mg sample of 2 dissolved in acetone-d_6 as before consisted of a single line with a chemical shift similar to that found for the enriched carbon of 1.

p-Aminobenzonitrile (5). p-Nitrobenzonitrile (4) (1.48 g; 0.01 mol) in 60 ml of 95% ethanol with 0.25 g. of platinum oxide was shaken under hydrogen at ca. atmospheric pressure until 890 ml of hydrogen had been consumed (theoretical 870 ml). The hydrogenation rate at this point was 10-15 ml per min. Filtration and evaporation gave 1.13 g. (9.58 mmol; 96%) of light orange-brown crystals (5) m.p. 71-80° (lit (2) 86°)

p-Acetyl-1-^{13}C-aminobenzonitrile (3) . The acetylation of 0.59 g. (5 mmol)

of 5 by the general acetylation procedure above gave 0.61 g. (3.9 mmol; 76%) of 3, m.p. 198-202° (lit (3) 202-203°). A 13.1 mg sample of 3 in acetone-d_6 as before revealed a single line at 169.1 ppm.

ACKNOWLEDGEMENT

This work was supported by U. S. Energy Research and Development Administration under Grant Number E(11-1)-2451 and the National Institutes of Health under Grant Number GM 08521-15. We are greatly indebted to Dr. Don K. Dalling for CMR spectra and discussions of these spectra.

REFERENCES

1. Williams J. W., Dickert Y. J., and Krynitsky J. A. - J. Amer. Chem. Soc. 63: 2510 (1941)
2. Heilbron I. M., Ed. - Dictionary of Organic Compounds (2nd Edition), Oxford University Press, New York, 1943
3. Jensen K. A. and Pedersen C. - Acta Chem. Scand. 15: 1104 (1961)
4. Friedman L. and Shechter H. - J. Org. Chem. 26: 2522 (1961)
5. Degnan W. M. and Shoemaker C. J. - J. Amer. Chem. Soc. 68: 104 (1946)
6. Good N. E. - Plant Physiol. 36: 788 (1961)
7. Dewar M. J. S. and Scott J. M. W. - J. Chem. Soc. 1957: 1445
8. Bergmann E. D. and Bentov M. - J. Org. Chem. 26: 1480 (1961)
9. Hibbert H. and Sturrock M. G. - J. Amer. Chem. Soc. 50: 3374 (1928)
10. Gisvold O. and Maulding H. V., Jr. - J. Pharm. Sciences, 57: 784 (1968)