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O-Acylation of Acidic Methylene Compounds

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We would like to report the results on the O-acylation of the relatively acidic methylene compound 1,2-diphenyl-4-butyl-3,5-pyrazolidinedione (phenylbutazone). The previously reported methods[1] which involved acylation in the presence of aqueous sodium hydroxide or triethylamine gave low yields of the *O*-acyl phenylbutazones (**2**) along with some uncharacterized side products. However, these results are not surprising in view of the fact that **2a** undergoes hydrolysis at a rate approaching that of acetic anhydride.[2] Carbon as well as oxygen acylation of the enolate of phenylbutazone is also possible and the C-acylated phenylbutazone may lead to some of the side products. Therefore, it was logical that methods used for preparing mixed anhydrides and *O*-acyl enolates offered the best opportunity for preparing **2**.

A recent innovation in the preparation of mixed anhydrides has been to employ the reaction of the thallium(I) salt of the weaker of the two acids with the acid halide of the stronger acid.[3a] In general, carbon acid thallium(I) salts are insoluble in most reaction solvents and in the case of phenylbutazone the insoluble nature of the thallous salt would ensure that an excess of the acid halide was always present in the reaction medium, conditions also known to maximize O-acylated product in the related reactions of enolate anions with acylating agents.[3b,4]

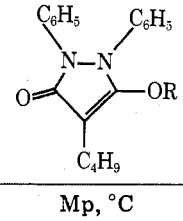
The thallium(I) salt of phenylbutazone (**1**) was a stable, nonhygroscopic white solid. Its infrared spectrum showed loss of all carbonyl bands exhibiting instead a broad absorption centered at 1500 cm^{-1} with a weak shoulder[5] at 1650 cm^{-1}. When **1** was suspended in ether and allowed to react with an acid chloride at room temperature, only one product was observed when the reaction was analyzed by TLC. The ir, uv, and NMR spectra, as well as the elemental analysis of the products were consistent with the corresponding *O*-acyl derivatives of phenylbutazone (**2**) and acid hydrolysis of several of the derivatives prepared regenerated phenylbutazone.

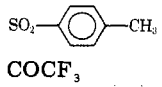
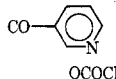
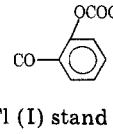
Attempts to prepare **2f** by reaction of **1**, or other salts of phenylbutazone, with nicotinoyl chloride hydrochloride in the presence or absence of an acid scavenger were unsuccessful. Apparently the intermediate acid chloride, generated in situ, preferentially reacted with itself to give an uncharacterized saltlike material faster than it reacted with **1** to give **2f**. Other amino acid chloride hydrochlorides gave similar results so that it was not possible to prepare **2** by the above route when R contained a tertiary amino group.

Therefore, an alternate synthetic scheme was investigated based on the observation of Bourne et al.[6] that 1:1 mixtures of trifluoroacetic anhydride (TFAA) and a carboxylic acid gave the corresponding mixed anhydride and pyridinium trifluoroacetate when the mixtures were allowed to react with pyridine. However, the initial reaction between phenylbutazone and TFAA did not give **2e**, but rather an incompletely characterized adduct that incorporated 1 equiv of TFAA[7] and is considered to be **3**. The NMR spectrum showed an acidic proton at δ 13.6 and loss of the methine hydrogen signal of O=C-CH-C=O centered at δ 3.4, and the ir spectrum showed two strong anhydride-like absorptions at 1830 and 1785 cm^{-1}, as well as complete loss of the carbonyl absorption at 1710 cm^{-1}.

More interesting was the fact that the initial adduct (**3**) could be equilibrated with another anhydride to give a second phenylbutazone adduct which had lost one trifluoroacetyl group and had incorporated the acyl portion of the other anhydride. Thus, **3** was equilibrated with acetic an-

Table I
***O*-Acyl Phenylbutazone Derivatives**

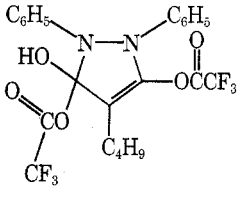


Compd	R	% yield	Mp, °C	Method[a]	Anal. Calcd over found
2a	$COCH_3$	54	49–51	TFAA	Experimental
2b	COC_6H_5	65	116–117.51[a]	Tl (I)	C, 75.70; H, 5.88; N, 6.79 C, 75.92; H, 5.85; N, 6.66
2c	$COC(CH_3)_3$	75	114–115	Tl (I)	Experimental
2d		33	125–126.5	Tl (I)	C, 67.51; H, 5.66; N, 6.06 C, 67.65; H, 5.74; N, 5.89
2e	$COCF_3$				
2f		78	139–141	TFAA	C, 72.62; H, 5.61; N, 10.16 C, 72.39; H, 5.64; N, 9.98
2g		54	85–871[b]	Tl (I)	C, 71.47; H, 5.57; N, 5.95 C, 71.26; H, 5.67; N, 5.82

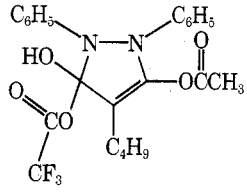
[a] TFAA and Tl (I) stand for the basic method used as exemplified in the Experimental Section for **2a** and **2c**.

hydride and the volatiles were removed in vacuo to give a crystalline adduct assigned structure **4**. Compound **2a** was then obtained by extracting a dichloromethane solution of **4** with 1 equiv of aqueous base and crystallizing **2a** from heptane; **2f** was prepared by the same method.

The infrared spectrum of **4** shows two carbonyl absorptions. One absorption at 1800 cm^{-1} is at the same position as the acetate carbonyl in **2a** and it has been assigned to the acetate carbonyl. The other carbonyl absorption at 1780 cm^{-1} is broad and shifted to longer wavelengths, which suggests that the trifluoroacetate carbonyl is involved in a hydrogen bond. Taken together, these assignments suggest the following structure for the adduct **4**. By analogy one may also infer a similar structure for **3**.



3



4

Experimental Section

General. All melting points were uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., and all analyses were within ±0.3%. TLC were run on Brinkmann polygram sil G/uv_{254}. NMR spectra were recorded on a Varian T-60 spectrometer using Me_4Si as an internal standard. Infrared spectra were recorded on a Beckman IR-33. Trifluoroacetic anhydride and thallium(I) ethoxide were obtained from Aldrich Chemical Co.

1,2-Diphenyl-4-butyl-5-acetyloxy-4-pyrazolin-3-one (2a). Phenylbutazone (5.0 g, 0.016 mol) was dissolved in 15.0 g (0.081 mol) of trifluoroacetic anhydride which was cooled with an ice bath; it usually took about 0.25 hr for all of the phenylbutazone to go into solution. Then the reaction mixture was concentrated in vacuo at room temperature to give **3** as a viscous, clear oil which crystallized when it was cooled in the refrigerator. The crystals were too hygroscopic to handle but NMR and ir spectra of the oil were recorded: ir (neat) 3000–2200 (broad, moderate) (O–H), 1830 (strong, sharp) (C=O), and 1780 cm^{-1} (broad, strong) (C=O); NMR ($CDCl_3$) δ 13.6 (1, 2, OH), 7.5–7.10 (10, m, aromatic H), 2.55–2.2 (2, m, CH_2C=), and 2.2–0.75 (7, m, CH_3 and CH_2). The oil was then allowed to react with 10 ml of acetic anhydride overnight in a tightly sealed flask under a nitrogen atmosphere. The volatile materials were evaporated at room temperature to give a white solid (mp 50–60°), a portion of which was recrystallized from CH_2Cl_2–heptane to give white crystals (mp 63–66°) of **4** whose spectral properties were identical with those of the crude solid: mp 50–60°; ir (KBr) 2800–2200 (broad, moderate) (O–H), 1800 (strong, sharp) (C=O), and 1780 cm^{-1} (broad, strong) (C=O); NMR ($CDCl_3$) δ 11.5 (1, s, OH), 7.55–7.0 (10, m, aromatic H), 2.5–2.1 (s, m, CH_2C=), 2.13 (3, s, CH_3C=O), and 2.1–0.75 (7, m, CH_3 and CH_2).

Anal. Calcd for $C_{23}H_{23}F_3N_2O_5$: C, 59.47; H, 4.99; N, 6.03; F, 12.27. Found: C, 59.54; H, 5.02; N, 6.18; F, 12.24.

The rest of the white solid, mp 50–60°, was dissolved in 120 ml of CH_2Cl_2 and extracted with 75 ml of water containing 1.7 g (0.017 mol) of $KHCO_3$. The CH_2Cl_2 layer was separated and dried over Na_2SO_4 and the CH_2Cl_2 was evaporated in vacuo to give a viscous light-yellow oil. The oil was crystallized from CH_2Cl_2–heptane (20:650) which was concentrated to 350 ml on a hot plate and then cooled in a refrigerator overnight to give 2.10 g (mp 49–51°) of **2a** as fine needles. The mother liquor was concentrated to 200 ml and cooled overnight to give an additional 0.93 g (mp 46–49°) of **2a** as fine needles for a total yield of **2a** of 54%: ir (KBr) 1800 and 1700 cm^{-1} (strong, sharp) (C=O); NMR ($CDCl_3$) δ 7.6–7.0 (10, m, aromatic H), 2.45–2.1 (2, m, CH_2-C=), 2.13 (3, s, CH_3C=O), and 2.0–0.7 (7, m, CH_3 and CH_2).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.97; H, 6.33; N, 7.99. Found: C, 71.79; H, 6.19; N, 8.16.

1,2-Diphenyl-4-butyl-5-pivaloxy-4-pyrazolin-3-one (2c). Thallium(I) ethoxide (2.24 g, 0.009 mol) was dissolved in anhydrous ether (100 ml) and allowed to react with 2.84 g (0.0092 mol) of phenylbutazone. The resulting white suspension was stirred at room temperature for 1 hr, and then it was filtered. The residue was dried in a vacuum desiccator to give 4.55 g (mp 194–202° dec) of the thallium(I) salt of phenylbutazone (1).

Anal. Calcd for $C_{19}H_{19}N_2O_2Tl$: C, 44.59; H, 3.74. Found: C, 44.26; H, 3.93.

A suspension of 1 (5.12 g, 0.01 mol) in anhydrous ether (100 ml) was then allowed to react with 1.20 g (0.01 mol) of pivalyl chloride. The resulting suspension was stirred at room temperature for 6 hr. Then it was filtered and the filtrate was concentrated in vacuo. The residue from the concentration of the filtrate was titrated with petroleum ether (bp 30–60°) to give 2.95 g (mp 114–115°, 75% yield) of **2c**: ir (KBr) 1790 and 1660 cm^{-1} (strong, sharp) (C=O); NMR ($CDCl_3$) δ 7.6–6.95 (10, m, aromatic H), 2.40–2.10 (2, m, CH_2C=C), 1.95–0.7 (7, m, CH_3 and CH_2), and 1.20 [9, s, $(CH_3)_3C$].

Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: 73.40; H, 7.06; N, 7.18.

Registry No.—**1**, 57091-21-1; **2a**, 57091-22-2; **2b**, 16006-72-7; **2c**, 57091-23-3; **2d**, 57091-24-4; **2f**, 57091-25-5; **2g**, 42177-40-2; **3**, 57091-26-6; **4**, 57091-27-7; phenylbutazone, 50-33-9; trifluoroacetic anhydride, 407-25-0; acetic anhydride, 108-24-7; thallium(I) ethoxide, 20398-06-5; pivalyl chloride, 3282-30-2; benzoyl chloride, 98-88-4; tosyl chloride, 98-59-9; 3-pyridinecarboxylic anhydride, 16837-38-0; 2-acetoxybenzoyl chloride, 5538-51-2.

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Electrolytic Decarboxylation Reaction. III. Anodic Acetoxylation of Tricyclo[4.4.0.0^{1,5}]decan-4-ones

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The conversion of carboxyl function to acetoxy group has been the subject of many investigations in recent years.[1-5] One of the major difficulties in the reaction is associated with lack of effective methods for preparing carbonium ion at the site of carbon atom attached to carboxyl group. Our interest in exploring the utility of the electrolytic decarboxylation method[6] enables us to investigate the electrochemical acetoxylation to carbonium ion at the C-2 carbon of the tricyclo[4.4.0.0^{1,5}]decan-4-one system. In this report we describe an application of the anodic acetoxylation method to the 2-carboxytricyclo[4.4.0.0^{1,5}]decan-4-ones (**1b** and **7**).

Electrolysis of **1b** in a mixed solvent of AcOH–*t*-BuOH–Et_3N (2:1:0.1) using platinum electrodes at a constant cur-