Acylation of *N'*-Arylbenzothiohydrazides and of their *N'*-Acyl-derivatives; 2-Acylalkylidene-3-aryl-5-phenyl-2*H*-1,3,4-thiadiazolenes and Related Compounds

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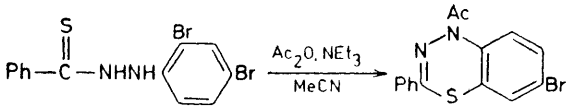
Reactions of *N'*-arylbenzothiohydrazides and of their *N*-acyl-derivatives with carboxylic anhydrides under various sets of conditions are shown to lead to 2-acylalkylidene-3-aryl-5-phenyl-2*H*-1,3,4-thiadiazolenes. The probable mechanism of formation of these compounds *via* the corresponding 2-alkylidenethiadiazolene as intermediate is discussed.

THE conversion of two substituted *N'*-arylbenzothiohydrazides to the corresponding 1-acetyl-1*H*-4,1,2-benzothiadiazines by boiling with a mixture of acetic anhydride, acetonitrile, and triethylamine has been reported previously.[1] While developing this as a



routine procedure, we soon became aware that the yields of thiadiazines were markedly sensitive to the quantity of acetic anhydride used. As the latter was increased significantly beyond the amount required for mono-acetylation of the thiohydrazide, the yield of thiadiazine decreased. An alternative product was being formed, corresponding in composition to addition of the unit C_4H_2O to the thiohydrazide. It was already known that these new products corresponded to an addition of two 'keten' units of C_2H_2O with concurrent loss of one unit of H_2O per molecule of the thiohydrazide involved. Our results at this stage are summarized in Table 1.

It can be seen from Table 1 that the presence of triethylamine is not essential to the reaction and that both the *N'*-arylbenzothiohydrazides and their *N'*-acetyl derivatives yield the same compounds in this reaction. The i.r. spectra of the new compounds all show a strong absorption band near 1 600 cm^{-1}, while their ^1H n.m.r. spectra show singlets at δ 2.1—2.2 (3 H, MeCO) and 5.5—5.6 (1 H, H–C=C) in addition to signals due to aromatically bound protons.

Our view of the course of these reactions is summarized in Scheme 1. To facilitate discussion, we have designated RCH_2CO as the acyl group first introduced and $R'CH_2CO$ as that introduced subsequently. Compound (2), resulting from acylation of (1), is thought to equili-

TABLE 1

Reactions of (1) and (2; R = H) with acetic anhydride to give 2-acylalkylidene-3-aryl-5-phenyl-2*H*-1,3,4-thiazdiazolenes (6)

Starting compound	Aryl group in (6)	Method	Yield (%)	M.p. (°C)	Formula [d]	Found (%) [Calc. (%)]
(1)	$C_6H_3I_2$-2,4	A [a]	45	186—187	$C_{17}H_{12}I_2N_2OS$	C, 37.5; H, 2.4; N, 5.0 [C, 37.4; H, 2.2; N, 5.1]
(1)	C_6H_3FI-2,4	A	43	185—186	$C_{17}H_{12}FIN_2OS$	C, 47.0; H, 3.0; N, 6.5; S, 7.3 [C, 46.6; H, 2.7; N, 6.4; S, 7.3]
(1)	$C_6H_3F_2$-2,4	A	67	196—197	$C_{17}H_{12}F_2N_2OS$	C, 62.1; H, 3.8; F, 11.3; N, 8.4 [C, 61.8; H, 3.6; F, 11.5; N, 8.5]
(2)	$C_6H_3F_2$-2,4	A	69	196—197	$C_{17}H_{12}F_2N_2OS$ [e]	
(2)	$C_6H_3Br_2$-2,4	A	94	154—155	$C_{17}H_{12}Br_2N_2OS$	C, 45.2; H, 2.8; Br, 35.2 [C, 45.1; H, 2.7; Br, 35.4]
(2)	$C_6H_3Br_2$-2,4	B [b]	94	155—156	$C_{17}H_{12}Br_2N_2OS$ [e]	
(1)	$C_6H_3Br_2$-2,5	C [c]	84	251—252	$C_{17}H_{12}Br_2N_2OS$	C, 44.9; H, 2.6; N, 6.2 [C, 45.1; H, 2.7; N, 6.2]
(1)	$C_6H_2Br_3$-2,4,6	B	100	218—219	$C_{17}H_{11}Br_3N_2OS$	C, 38.3; H, 1.9; N, 5.3 [C, 38.4; H, 2.1; N, 5.3]
(1)	C_6H_4Br-4	B	49	186—187	$C_{17}H_{13}BrN_2OS$	C, 54.6; H, 3.6; N, 7.3; S, 8.4 [C, 54.5; H, 3.5; N, 7.5; S, 8.6]

[a] Reflux with acetic anhydride in acetonitrile–triethylamine for 15—60 min. [b] Reflux with acetic anhydride for 60 min. [c] Reflux with acetic anhydride in acetic acid for 60 min. [d] Analytical samples were crystallized from ethanol, where necessary after chromatography on Florisil. [e] Unchanged on attempted hydrolysis by refluxing with ethanol–concentrated HCl for 1.5—3 h.

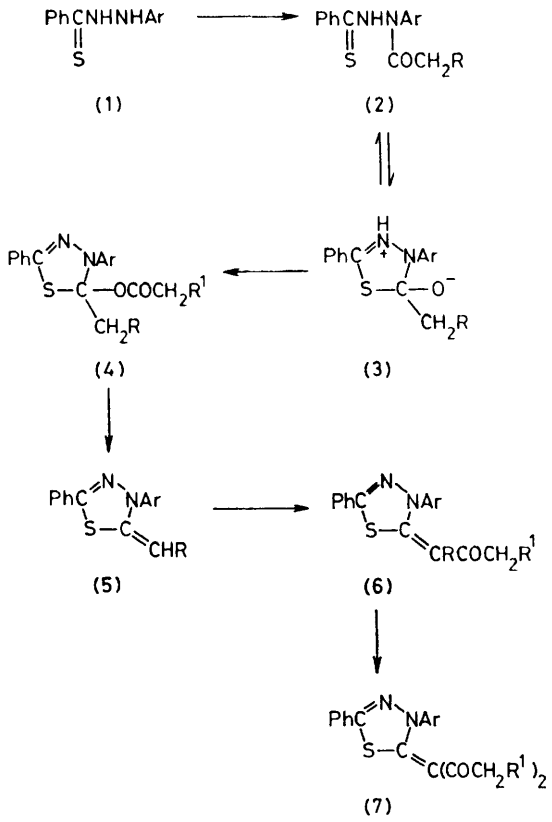
the product of monoacetylation of *N'*-arylbenzothiohydrazides (1) by acetic anhydride is the *N'*-acetyl derivative (2; R = H). The overall process leading to

$$\underset{(1)}{PhCSNHNHAr} \longrightarrow \underset{(2)}{PhCSNHN(COCH_2R)Ar}$$

brate with species (3) which is then acylated with proton loss to (4). Loss of carboxylic acid ($R'CH_2CO_2H$), presumably by ionization and proton loss, to give (5) is then followed by acylation of the electron-rich double bond to give the thiadiazolene (6). It has in fact been possible to terminate this sequence at compound (5) for a

case in which R = R′ = 4-nitrophenyl; the yield of (5) from the reaction of (1; Ar = 2,4-dibromophenyl) with 4-nitrophenylacetyl chloride in benzene is optimal when two equivalents of the acid chloride are used, as would be expected. It has also been possible to extend the sequence from (6) to (7) by refluxing (1; Ar = Ph) with a large excess of acetic anhydride; this gives (7; Ar = Ph, R′ = H) as the major product, with (6; Ar = Ph; R = R′ = H) as minor product, following a modified isolation procedure.

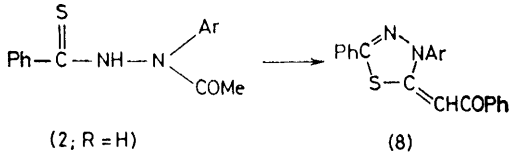
In order to explore further the scope of the reactions leading from (1) to (6), we have separated the acylation steps and have prepared *N*′-acetyl and *N*′-propionyl derivatives (2) of two *N*′-arylbenzothiohydrazides (1).



SCHEME 1

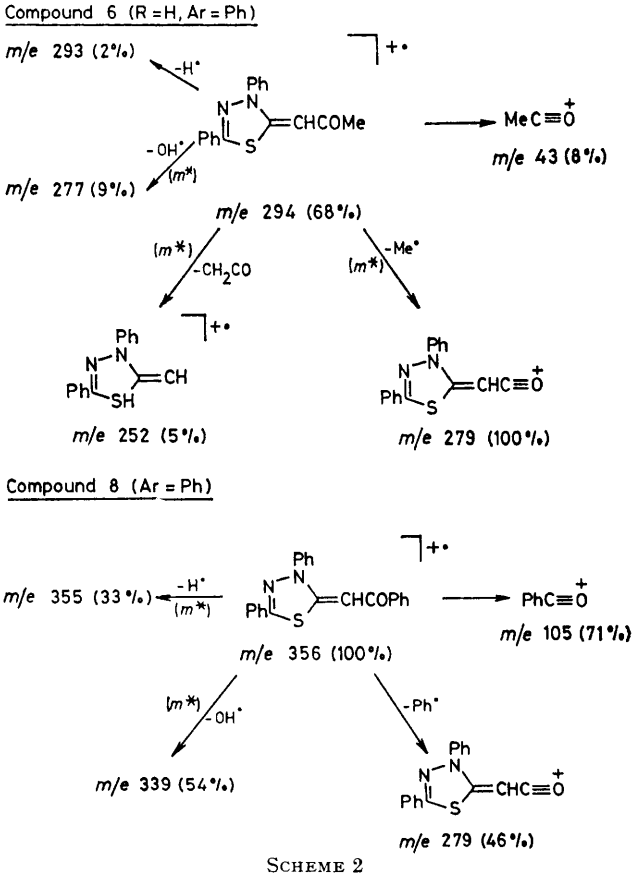
We note in passing that the ^{1}H n.m.r. spectra of these compounds (2) exhibit a number of features of interest, suggestive of hydrogen bonding and of the presence of more than one conformer in solution. Thus several of the compounds (2; R = H, Ar = 2,4-dihalogenophenyl) show both the methyl and N–H signals as doublets (in deuteriochloroform), the former remaining and the latter disappearing on deuterium oxide exchange. The spectrum of (2; R = H, Ar = 2,4-dibromophenyl) in [$^2H_6$]-dimethyl sulphoxide is similar to that in deuteriochloroform except that the doublet methyl peaks are no longer of (approximately) equal intensity; peak coalescence occurs in each solvent at *ca.* 70 °C. In the unsubstituted compound (2; R = H, Ar = Ph), doublets are seen for methyl and N–H protons when the sample is cooled (to −50 °C). The propionyl derivative (2; R = Me, Ar = 2,4-dibromophenyl) shows a complex splitting pattern for the ethyl group, possibly an ABX_3 spin system superimposed on an A_2X_3 spin system, together with the N–H signal as a doublet.

Each of the foregoing acyl derivatives (2) was acylated using acetic and propionic anhydrides, respectively. The results obtained were in each case consistent with product formulation as (6) in Scheme 1. Analogous compounds (8) were formed when benzoic anhydride was used in place of acetic or propionic anhydride.



(2; R = H) (8)

In those cases for which R = R′, conversion of (1) to (6) (Scheme 1) may usually be achieved in one stage, *e.g.* by refluxing (1) with acetic anhydride (for R = R′ = H). It is probable that these acylations can be achieved with various other acylating agents. For example, we have noted conversion of (1; Ar = 2,4-dibromophenyl) to (6; R = R′ = H, Ar = 2,4-dibromophenyl) by refluxing with diketen in benzene.

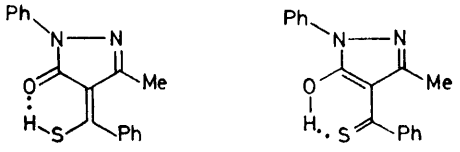


SCHEME 2

The mass spectra of compounds (6) and (8) show molecular ions whose fragmentations generally follow the patterns shown for the prototypes (6; R = H,

Ar = Ph) and (8; Ar = Ph) in Scheme 2. It appears that cleavage at the carbonyl function is the favoured process in the initial fragmentation, one route predominating with the acetyl and the other with the benzoyl derivative. An unusual feature of the initial fragmentation is the loss of HO· from the molecular ion, particularly from the benzoyl derivative. This situation is reminiscent of a similar loss observed in the mass spectra of certain α-(1,2-dithiol-3-ylidene)ketones and the resulting ion may form in an analogous way.[2] Among the subsequent fragmentations, loss of PhCSN from the ion *m/e* 279 seems to be the most significant, a metastable ion being observed in the case of the benzoyl derivative (8; Ar = Ph). The presence of PhS, PhCS, and PhCN ions is also evident and is consistent with their appearance in the mass spectra of simpler thiadiazolenes.[3]

The present syntheses make this group of thiadiazolenes (6) and (8) reasonably accessible. Previous direct methods have been based on the reaction of appropriately substituted thiadiazolene-5-thiones with diazoacetophenone,[4] or on the reaction of hydrazonoyl halides with β-ketothioanilides in the presence of base.[5] We have correlated 2-benzoylmethylene-3,5-diphenyl-2*H*-1,3,4-thiadiazolene (8; Ar = Ph) with one cited in the former



(9)

work.[4] There is also a recent report of the formation of 5-methyl-2-phenyl-1-thiobenzoylpyrazol-3(2H)-one from reaction of (1; Ar = Ph) and of the corresponding hydrazonoyl disulphide with acetic anhydride in pyridine.[6] The properties of this material tally with those of (6; R = R′ = H, Ar = Ph) and the compound should be redesignated as this thiadiazolene. We note incidentally that the parent 3-methyl-1-phenylpyrazol-5-one yields a thiobenzoyl derivative when treated with thiobenzoylthioglycolic acid in presence of base. This is considered to be the 4-thiobenzoylpyrazolone in one of its possible tautomeric, hydrogen-bonded forms, *e.g.* (9).

EXPERIMENTAL

I.r. data were recorded for KBr discs. ^{1}H N.m.r. spectra were obtained at ambient temperature in deuteriochloroform as solvent (tetramethylsilane as internal standard) on a Varian A60 or Bruker WP60 Fourier-transform n.m.r. spectrometer. Mass spectra were obtained on an AEI MS30 double beam instrument and *m/e* values are recorded for the lowest isotopic species (relative intensities in parentheses).

Acetylation of (1) *and* (2; R = H); *General Methods*.—(A) Compound (1; Ar = 2,4-difluorophenyl) [1] (1.5 g) was dissolved by boiling in acetonitrile (10 ml) and a hot mixture of acetic anhydride (14 ml) and triethylamine (11.8 ml) was added. The mixture was refluxed for 45 min and then cooled (ice-bath), whereupon the product separated.

(B) Compound (2; R = H, Ar = 2,4-dibromophenyl) [1] (1.0 g) and acetic anhydride (8 ml) were refluxed for 1 h. When cool, excess water was added and the product was collected, dried, and chromatographed (Florisil; chloroform) prior to crystallization.

(C) Compound (1; Ar = 2,5-dibromophenyl) [7] (2.0 g), glacial acetic acid (10 ml), and acetic anhydride (10 ml) were refluxed for 1 h. The product was isolated as in Method B.

2-(4-*Nitrophenylmethylene*)-3-(2,4-*dibromophenyl*)-5-*phenyl*-2H-1,3,4-*thiadiazolene* (5; R = 4-*nitrophenyl*, *Ar* = 2,4-*dibromophenyl*).—Compound (1; Ar = 2,4-dibromophenyl) (1.0 g) and 4-nitrophenylacetyl chloride (1.04 g) in dry benzene (10 ml) were refluxed for 30 min. After cooling, the precipitate was collected, washed with benzene, and dried (960 mg, 69%), m.p. 265—268 °C. Crystallization from pyridine–methanol afforded the *product* as red prisms, m.p. 268—270 °C (Found: C, 47.5; H, 2.4; N, 7.8. $C_{21}H_{13}Br_2N_3O_2S$ requires C, 47.5; H, 2.5; N, 7.9%); *m/e* 529 (11%, M^+) and 121 (100, PhCS).

Extended Acetylation of (1; *Ar* = *Ph*).—A solution of (1; Ar = Ph) (1.35 g) in acetic anhydride (15 ml) was refluxed for 1 h. When cool, the mixture was poured into water, and the organic products were extracted with benzene. Drying, evaporation, and chromatography (silica gel; toluene) gave a trace of gum, followed by (6; R = R′ = H, Ar = Ph) (150 mg, 9%), m.p. 151—153 °C (lit.,[6] 152—153 °C) (from ethanol). Continued elution gave *compound* (7; R′ = H, Ar = Ph) (650 mg, 32%), which crystallized from ethanol as needles, m.p. 192—193 °C (Found: C, 67.6; H, 4.9; N, 8.2; S, 9.2. $C_{19}H_{16}N_2O_2S$ requires C, 67.9; H, 4.8; N, 8.3; S, 9.5%); mass spectrum *m/e* 336 (31%, M^+) and 279 (100); δ 2.04 (s, 6 H, Me).

Preparation of N′-*Acyl*-N′-*arylbenzothiohydrazides* (2).—(*a*) Acetyl chloride (1.7 ml) was added slowly to a solution of (1; Ar = 2,4-dibromophenyl) (8.0 g) in dry pyridine (50 ml) at 0° C. The resulting mixture was then stirred for 2 h at room temperature, after which it was poured into water (500 ml). Crystallization from ethanol afforded (2; R = H, Ar = 2,4-dibromophenyl) (7.0 g, 78%) as yellow prisms, m.p. 176—178 °C (lit.,[7] 177—178 °C).

(*b*) Similar treatment of (1; Ar = Ph) (2.3 g) in pyridine (20 ml) with acetyl chloride (0.8 ml) afforded (2; R = H, Ar = Ph) (2.1 g, 78%), m.p. 147—150 °C (lit.,[8] 154 °C) (benzene–hexane).

(*c*) Similar treatment of (1; Ar = 2,4-dibromophenyl) (8.0 g) in pyridine (50 ml) with propionyl chloride (2.0 ml) afforded N′-(2,4-*dibromophenyl*)-N′-*propionylbenzothiohydrazide* (2; R = Me, Ar = Ph) (8.6 g, 94%) as yellow prisms, m.p. 157—159 °C (ethanol) (Found: C, 43.8; H, 3.3; N, 6.3. $C_{16}H_{14}Br_2N_2OS$ requires C, 44.0; H, 3.2; N, 6.3%); $\nu_{max.}$ 3 200 (N–H) and 1 660 cm^{-1} (C=O); δ 1.0—1.5 (m, 3 H, CH_2Me), 2.0—3.0 (m, 2 H, $COCH_2Me$), 7.2—8.2 (m, 8 H, arom.), 9.3 and 9.7 (d, 1 H, –NH–); mass spectrum *m/e* 440 (<0.1%, M^+), 423 (7, $M^+ - OH$), and 77 (100, Ph).

(*d*) Benzoyl chloride (0.4 ml) was added to a stirred solution of (1; Ar = 2,4-dibromophenyl) (1.0 g) in water (20 ml) containing a sodium hydroxide pellet. After being stirred for 30 min, a few drops of acetic acid were added to coagulate the colloidal suspension. The precipitate was collected, washed with water, and then dried. Crystallization from methylene chloride–hexane gave N′-*benzoyl*-N′-(2,4-*dibromophenyl*)*benzothiohydrazide* (940 mg, 75%) as small yellow needles, m.p. 127—129 °C (Found: C, 48.8; H, 3.0; N, 5.5. $C_{20}H_{14}Br_2N_2OS$ requires C, 49.0; H, 2.9; N,

5.7%); $\nu_{max.}$ 3 220 (N–H) and 1 665 cm^{-1} (C=O); δ 7.2—8.2 (m 13 H, arom.), 10.0 (s, 1 H, –NH–); *m/e* 488 (1%, M^+), 471 (*ca.* 0.1, M^+ – OH), and 105 (100, PhCO).

Reactions of N′-Acyl-N′-arylbenzothiohydrazides (2) *with Different Acid Anhydrides.*—(*a*) Compound (2; R = H, Ar = 2,4-dibromophenyl) was converted to (6; R = R′ = H, Ar = 2,4-dibromophenyl) by Method B.

(*b*) Compound (2; R = H, Ar = 2,4-dibromophenyl) (1.0 g) in a mixture of propionic anhydride (3 ml) and acetonitrile (3 ml) was refluxed for 2 h. The usual work-up followed by crystallization from 95% ethanol gave *compound* (6; R = H, R′ = Me, Ar = 2,4-dibromophenyl) (690 mg, 63%) as tan coloured needles, m.p. 117—118 °C (Found: C, 46.5; H, 3.0; N, 6.0. $C_{18}H_{14}Br_2N_2OS$ requires C, 46.4; H, 3.0; N, 6.0%).

(*c*) Compound (2; R = Me, Ar = 2,4-dibromophenyl) (1.0 g) in acetic anhydride (10 ml) was refluxed for 1 h. The usual work-up followed by crystallization from benzene–hexane afforded *compound* (6; R = Me, R′ = H, Ar = 2,4-dibromophenyl) (790 mg, 74%) as pale yellow prisms, m.p. 169—172 °C (Found: C, 46.1; H, 3.0; N, 5.9. $C_{18}H_{14}Br_2N_2OS$ requires C, 46.4; H, 3.0; N, 6.0%).

(*d*) Compound (2; R = Me, Ar = 2,4-dibromophenyl) (2.0 g) in a mixture of propionic anhydride (3 ml) and acetonitrile (3 ml) was refluxed for 2 h. On cooling, the solution deposited *compound* (6; R = R′ = Me, Ar = 2,4-dibromophenyl) (1.96 g, 93%) as yellow prisms, m.p. 182—185 °C. Crystallization from benzene–hexane gave material of m.p. 183—185 °C (Found: C, 47.5; H, 3.3; N, 5.6. $C_{19}H_{16}Br_2N_2OS$ requires C, 47.5; H, 3.4; N, 5.8%).

(*e*) Compound (2; R = H, Ar = 2,4-dibromophenyl) (1.9 g) in acetonitrile (10 ml) containing benzoic anhydride (5.3 g) was refluxed for 3 h. After cooling, 10% sodium hydroxide (60 ml) was added and the solution stirred for 2 h. The orange precipitate which separated was collected, washed with water, and dried. Column chromatography on silica gel, using benzene as eluant, followed by crystallization from acetonitrile, afforded *compound* (8; Ar = 2,4-dibromophenyl) (1.66 g, 73%) as yellow prisms, m.p. 168—170 °C (Found: C, 51.4; H, 2.8; N, 5.4. $C_{22}H_{14}Br_2N_2OS$ requires C, 51.4; H, 2.7; N, 5.5%).

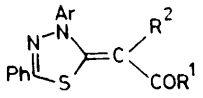
(*f*) Compound (2; R = H, Ar = Ph) (1.0 g) in pyridine (10 ml) containing benzoic anhydride (4.2 g) was refluxed for 1 h. The brown solution was then poured into water (200 ml) containing sodium hydroxide (5 g) and the precipitate obtained upon stirring was collected. Column chromatography on silica gel, using benzene as eluant, followed by crystallization from acetonitrile, afforded (8; Ar = Ph) (820 mg, 62%) as pale orange prisms which melted at 160—162 °C, re-solidified, and melted again at 169—170 °C. A sample crystallized from ethanol as short yellow needles, m.p. 170—171 °C (lit.,[4] 170 °C).

(*g*) Compound (6; R = R′ = H, Ar = Ph), required for completeness, was prepared from (1; Ar = Ph) by Method B (65% yield) and had m.p. 150—152 °C (lit.,[6] 152—153 °C).

Relevant i.r. and ^1H n.m.r. data for compounds prepared in (*a*) above are shown in Table 2.

Alternative Synthesis of (6; R = R′= H, Ar = 2,4-*dibromophenyl*).—Compound (1; Ar = 2,4-dibromophenyl) (1.0 g) in benzene (10 ml) containing diketen (1 ml) was refluxed overnight. The solvent was evaporated and the residual brown oil taken up in acetonitrile. This gave the product (702 mg, 60%) as yellow prisms, m.p. 148—154 °C. Successive recrystallizations gave material of m.p. and mixed m.p. 155—157 °C.

TABLE 2

I.r. and ^1H n.m.r. data for 

Substituents Ar	R¹	R²	ν(C=O)/ cm^{-1}	δ Non-aromatic protons
$C_6H_3Br_2$-2,4	Me	H	1 615	R¹ 2.12 R² 5.45
$C_6H_3Br_2$-2,4	CH_2Me	H	1 600	R¹ 1.13 (t), 2.41 (q) (*J* 7.2 Hz) R² 5.47
$C_6H_3Br_2$-2,4	Me	CH_3	1 600	R¹ 2.25 R² 1.55
$C_6H_3Br_2$-2,4	$MeCH_2$	CH_3	1 600	R¹ 1.17 (t), 2.52 (q) (*J* 7.0 Hz) R² 1.55
$C_6H_3Br_2$-2,4	Ph	H	1 595	R² 6.16
Ph	Ph	H	1 600	R² 6.70
Ph	Me	H	1 600	R¹ 2.17 R² 6.10

Thiobenzoylation of 3-Methyl-1-phenylpyrazol-5-one.—A solution of 3-methyl-1 phenylpyrazol-5-one (2.0 g) and thiobenzoylthioglycolic acid (2.44 g) in 50% methanol (50 ml) containing sodium hydroxide (1.0 g) was refluxed for 30 min. The solution was allowed to cool and then acidified with acetic acid (10 ml). The precipitate which formed was crystallized from ethanol. This afforded *3-methyl-1-phenyl-4-thiobenzoylpyrazol-5-one* (610 mg, 18%) as yellow needles, m.p. 105—107 °C (Found: C, 69.1; H, 4.8; N, 9.5. $C_{17}H_{14}N_2OS$ requires C, 69.4; H, 4.8; N, 9.5%); $\nu_{max.}$ 1 600, 1 540, 1 500, 1 480, 1 425, 980, 770, and 705 cm^{-1}; δ 1.83 (s, 3 H, =C–Me), 7.3—8.1 (m, 10 H, arom.), and 14.16 (s, 1 H, exchangeable with D_2O); *m/e* 294 (34%, M^+), 293 (100, M^+ – H), 277 (5, M^+ – OH), 261 (92, M^+ – SH), 233 (4, 261-CO), 180 (3), 175 (4), and 161 (4).

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