Reaction of Acylhydrazines with Phenyltrichloromethane; A Simple Synthesis of *N*-Acyl-phenylmethanehydrazonates and 1,3,4-Oxadiazoles

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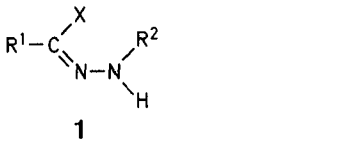
Hydrazonoyl halides **1** (X = Cl, Br) are potentially useful intermediates in heterocyclic chemistry. The most direct synthesis involves bromination of hydrazones[1,2] but is subject to severe limitations[3]. Other methods involve reaction of phosphorus pentachloride[3] or triphenylphosphine/carbon tetrachloride[4] with a monohydrazide.

We considered that the hydrazonoyl chloride **1** (X = Cl, $R^1 = C_6H_5$) might be formed *in situ* by reaction of *N*-acyl- or *N*-aroylhydrazines **3** with the readily available phenyltrichloromethane **(2)**. Although no direct evidence for the formation of the hydrazonoyl chloride **1** could be obtained, we have found that this reaction provides a simple access to esters of *N*-acyl-phenylmethanehydrazonic acids **4** and 2,5-disubstituted 1,3,4-oxadiazoles **5**.



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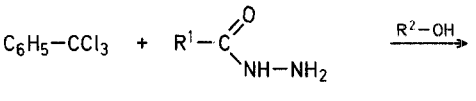
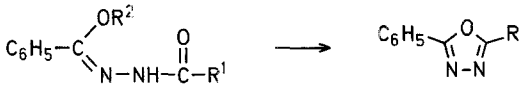
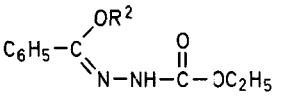


2 **3a** R^1 = alkyl; **b** R^1 = aryl; **c** $R^1 = OC_2H_5$



4a R^1 = alkyl; **b** R^1 = aryl; **c** $R^1 = OC_2H_5$ — **5a** R^1 = alkyl; **b** R^1 = aryl



4c

6 **7**

Reaction of *N*-acylhydrazines **3a** with an equimolar amount of phenyltrichloromethane **(2)** under reflux for 8 h in a primary alcohol (except methanol) in the presence of anhydrous sodium carbonate gives the esters of *N*-acyl-phenylmethanehydrazonic acids **4**. Although the yields of **4** are only moderate (30–50%), the present method provides a convenient, one-pot synthesis of **4a** which compares favourably with the known, multi-step preparations[2,5,6,7] of similar compounds (Table 1).

Products **4a** were characterised by ^{1}H-N.M.R., I.R., and mass spectrometry. The characteristic fragments in the mass spectra correspond to the cleavage of the R^2 group ($m/e = M - R^2 + 1$), the R^2O group ($m/e = M - R^2 - 16$), and R^2—OH ($m/e = M - R^2 - 17$). The last fragment probably originates from a thermal elimination.

On heating in the absence of a solvent at 205–210°, compounds **4a** undergo cyclisation to give the known 2-alkyl-5-

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Table 1. *N*-Acyl- and *N*-Ethoxycarbonyl-phenylmethanehydrazonates **4a** and **4c**

Product No.	R^1	R^2	Yield [%]	m.p.	Molecular formula[a]	I.R. (KBr)[b] $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$)[c] δ [ppm]
4a	H_3C	C_2H_5	31	102°	$C_{11}H_{14}N_2O_2$ (206.2)	1655	1.32 (t, 3H, OCH_2CH_3); 2.30 (s, 3H, $CO-CH_3$); 4.0 (q, 2H, OCH_2CH_3)
4a	H_3C	n-C_3H_7	41	78.5°	$C_{12}H_{16}N_2O_2$ (220.3)	1660	0.98 (t, 3H, $CH_2CH_2CH_3$); 2.32 (s, 3H, $CO-CH_3$); 3.92 (t, 2H, OCH_2)
4a	H_3C	n-C_4H_9	46	63.5°	$C_{13}H_{18}N_2O_2$ (234.3)	1675	0.93 (t, 3H, CH_2CH_3); 2.32 (s, 3H, $CO-CH_3$); 3.93 (t, 2H, OCH_2)
4a	C_2H_5	C_2H_5	32	82°	$C_{12}H_{16}N_2O_2$ (220.3)	1660	1.22 (t, 3H, $CO-CH_2CH_3$); 1.33 (t, 3H, $O-CH_2CH_3$); 2.68 (q, 2H, $CO-CH_2CH_3$); 3.97 (q, 2H, $O-CH_2CH_3$)
4a	n-C_3H_7	C_2H_5	49	68°	$C_{13}H_{18}N_2O_2$ (234.3)	1660	0.97 (t, 3H, $CO-CH_2CH_3$); 1.37 (t, 3H, $O-CH_2CH_3$); 2.87 (t, 2H, $CO-CH_2CH_2$); 3.97 (q, 2H, $O-CH_2CH_3$)
4c	C_2H_5O	C_2H_5	33	81°	Lit.[5] m.p. 80°	1730–1710	1.30 (t, 6H, $O-CH_2CH_3$ + $CO-OCH_2CH_3$); 3.93 (q, 2H, $O-CH_2-$); 4.20 (q, 2H, $CO-O-CH_2$)

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.30, H ±0.20, N ±0.20). The mass spectra (Varian CH5 spectrometer) are in accord with these structures.

[b] Perkin-Elmer 257 spectrometer.

[c] Spectra recorded at 60 MHz with a Varian T-60 spectrometer. The products can exist as (*E*)- or (*Z*)-isomers. The reported spectra of methyl *N*-tosyl-phenylmethanehydrazonates[8] and of phenylhydrazones[9] suggest that these isomers should give signals separated by ~0.1 ppm for the $O-CH_2-$ protons of the OR^2 group. In all spectra, only 1 signal (t or q) was observed for these methylene protons, suggesting that the products are configurationally homogeneous. The stereochemistry was not further investigated.

Table 2. Reaction of Phenyltrichloromethane (**2**) with *N*-Aroylhydrazines **3b** in Ethanol

R^1	Reflux time [h]	Yield [%] of **5b**	m.p.	Lit. m.p.
C_6H_5	6	75	139.5°	138°[12,13]
$4\text{-}O_2N-C_6H_4$	14	67	209°	207–209°[11,12]
$4\text{-}H_3CO-C_6H_4$	24	90	146.5°	146°[11,12]
$4\text{-}Cl-C_6H_4$	24	84	162°	162°[11,12]

phenyl-1,3,4-oxadiazoles **5a** in yields exceeding 95%. When methanol is used as solvent for the reaction of **2** with **3a**, 2-methyl-5-phenyl-1,3,4-oxadiazole **5a** ($R^1=CH_3$) is obtained directly in 31% yield.

Reactions of **2** with *N*-aroylhydrazines **3b** under reflux lead directly to the 2-aryl-5-phenyl-1,3,4-oxadiazoles **5b** in yields of >70%. These yields are better than those obtained by cyclisation of a dihydrazide[11]; this method can also be used for the preparation of unsymmetrically substituted 1,3,4-oxadiazoles. The intermediates **4b** are not isolated but are known to be rapidly converted to **5b** under the reaction conditions[12] (Table 2).

The reaction of *N*-ethoxycarbonylhydrazine (**3c**, $R^1=OC_2H_5$) with **2** leads to **4c** which does not undergo thermal cyclisation. However, treatment of compound **4c** with thionyl chloride readily brings about cyclisation and consecutive demethylation of the 1,3,4-oxadiazole **6** to give 5-oxo-2-phenyl-4,5-dihydro-1,3,4-oxadiazole (**7**).

Hydrazonyl chlorides **1** (X=Cl, $R^1=C_6H_5$, R^2=acyl or aroyl) have not been detected and the mechanism of formation of **4** certainly involves several steps. However, in view of the analogous reactions of imidoyl chlorides with alcohols to give imidates[14], **1** is probably one of the intermediates. An alternative method involves conversion of **2** to triethyl orthobenzoate [$C_6H_5-C(OC_2H_5)_3$] which, on reaction with the hydrazine, give the 1,3,4-oxadiazole in analogy to Ainsworth's classical synthesis[15]. The latter mechanism has been ruled out on the basis of the following control experiments:

- Reaction of **2** in refluxing ethanol in the presence of sodium carbonate gives only ethyl benzoate; no trace of triethyl orthobenzoate, which is stable under these conditions, could be detected in the ^{1}H-N.M.R. spectrum;
- Ethyl benzoate does not react with benzoylhydrazine;
- The reaction of triethyl orthobenzoate with benzoylhydrazine to give 2,5-diphenyl-1,3,4-oxadiazole (**5b**, $R^1=C_6H_5$) is much slower than the analogous reaction of **2** with **3b**.

N-Acyl-phenylmethanehydrazonic Acid Esters 4:
Phenyltrichloromethane (**2**; 1.95 g, 10 mmol), the *N*-acylhydrazine **3** (10 mmol), anhydrous sodium carbonate (2.15 g, 20 mmol), and the primary alcohol (50 ml) are heated under reflux for 8 h. The suspension is filtered while hot and the solvent evaporated. The oily residue is dissolved in ether, the ether solution is washed several times with water, dried with sodium sulphate, filtered, and evaporated. The residue is recrystallised from the minimum amount of petroleum ether.

Thermal Rearrangement of 4 to 1,3,4-Oxadiazoles 5:
The respective compound **4** is heated at 205–210° in a sealed tube in the absence of a solvent for 1 h. The residue is purified by distillation or recrystallisation; yield: >95%.

2-Methyl-5-phenyl-1,3,4-oxadiazole (**5a**, $R^1=CH_3$); m.p. 67° (methanol); Lit.[15] m.p. 67–68°.

2-Ethyl-5-phenyl-1,3,4-oxadiazole (**5a**, $R^1=C_2H_5$); b.p. 127°/20 torr; Lit.[15], b.p. 105°/0.1 torr.

Ethyl *N*-Ethoxycarbonyl-phenylmethanehydrazonate (4c; $R^1=OC_2H_5$, $R^2=C_2H_5$):
Phenyltrichloromethane (**2**; 1.95 g, 10 mmol), ethoxycarbonylhydrazine (**3c**; 1.56 g, 15 mmol), anhydrous sodium carbonate (1.5 g, 14 mmol), and ethanol are heated under reflux for 10 h. After treatment as described above, the petroleum ether solution is maintained at 0° for 3 days. The precipitate is filtered and recrystallised from petroleum ether; yield: 0.78 g (33%); m.p. 81°; Lit.[5] m.p. 80°.

5-Oxo-2-phenyl-4,5-dihydro-1,3,4-oxadiazole (7):
Compound **4c** (1.18 g, 5 mmol), thionyl chloride (4 ml), and toluene (3 ml) are heated under reflux until evolution of hydrogen

chloride ceases. The mixture is allowed to cool, is poured on to crushed ice, and allowed to stand for 2 h. The resultant mixture is extracted with ether, the ether solution is washed with water, dried with sodium sulphate, and evaporated. The oily residue which crystallises rapidly is recrystallised from benzene; yield: 0.41 g (51%); m.p. 139°; Lit. [16] m.p. 138°.

2-Aryl-5-phenyl-1,3,4-oxadiazoles 5b from *N*-Aroylhydrazines 3b: Phenyltrichloromethane (**2**; 3.9 g, 20 mmol), *N*-aroylhydrazine **3b** (20 mmol), anhydrous sodium carbonate (2 g, 19 mmol), and a primary alcohol (50 ml) are heated under reflux for the time given in Table 2. The mixture is then filtered while hot, the alcohol is evaporated, and the residue recrystallised from ethanol.

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[1] J. B. Aylward, F. L. Scott, *J. Chem. Soc.* [B] **1969**, 1080.
[2] F. L. Scott, M. Cashman, A. F. Hegarty, *J. Chem. Soc.* [B] **1971**, 1607 and literature cited therein.
[3] M. T. McCormack, A. F. Hegarty, *J. Chem. Soc. Perkin Trans. 2* **1976**, 1701.
[4] P. Wolkoff, *Can. J. Chem.* **53**, 1333 (1975).
[5] M. Pesson, S. Dupin, M. Antoine, *Bull. Soc. Chim. Fr.* **1962**, 1364.
[6] H. Weidinger, J. Kranz, *Chem. Ber.* **96**, 1049 (1963).
[7] M. F. Betkouski, M. Lwowski, *J. Chem. Soc. Chem. Commun.* **1973**, 932.
[8] R. J. Crawford, R. Raap, *Can. J. Chem.* **43**, 126 (1965).
[9] G. J. Karabatsos, R. A. Taller, *J. Am. Chem. Soc.* **85**, 3624 (1963).
[10] M. Golfier, M. G. Guillerez, *Tetrahedron Lett.* **1976**, 267.
[11] A. P. Grekov, N. L. Kulakova, O. P. Schvaika, *Zh. Obshch. Khim.* **29**, 3054 (1959); *C. A.* **54**, 13108 (1960).
[12] R. Milcent, C. Redeuilh, *J. Heterocycl. Chem.* **14**, 53 (1977).
[13] E. Steininger, *Monatsh. Chem.* **97**, 1195 (1966).
[14] R. Bonnett, in *The Chemistry of the Carbon-Nitrogen Double Bond*, Interscience, London, 1970, Chapter 13.
[15] C. Ainsworth, *J. Am. Chem. Soc.* **77**, 1148 (1955).
[16] A. Dornow, K. Brunken, *Chem. Ber.* **92**, 527 (1959).

0039-7881/79/1232-0948 $ 03.00