Tetrahedron. Vol. 29, pp. 121 to 124. Pergamon Press 1973. Printed in Great Britain

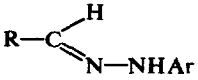
REACTION OF CARBANIONS OF β-DIKETONES AND β-KETO ESTERS WITH HYDRAZIDIC BROMIDES

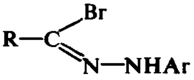
A. S. SHAWALI and H. M. HASSANEEN
Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

(*Received in the UK* 1 *June* 1972; *Accepted for publication* 20 *August* 1972)

Abstract—The carbanions of acetylacetone, dibenzoylmethane, ethyl acetoacetate and ethyl benzoylacetate react with hydrazidic bromides (2) in ethanol at room temperature to give substituted pyrazoles (3–6) respectively in good yields. The procedure appears to be a convenient and unequivocal method for preparing a particular pyrazole isomer. The structure assignments of the compounds prepared were based on elemental analyses and spectral and chemical evidence.

The direct bromination of aldehyde arylhydrazones (1) in acetic acid leads to the replacement of the methine hydrogen and the formation of the hydrazidic bromides (2).[1–14] In this reaction, derivatives of a variety of substituted hydrazines,[3–6] and of aldehydes[2,7–9] have been used. Within the past 10 years, the use of the products (2) as precursors for the 1,3-dipolar ions[10–12] and azocarbonium ions,[4,13–15] which have been demonstrated to undergo a wide variety of reactions, has been extensively studied. In spite of this wide application of hydrazidic bromides in synthetic studies, no information is available concerning their reaction with the conjugate bases of active methylene compounds. Here we report our study on the reactions of 2 (Ar as $4\text{-}NO_2C_6H_4$, R variable) with the carbanions of acetylacetone, dibenzoylmethane, ethyl acetoacetate and of ethyl benzoylacetate. The results are formulated in Scheme 1. The physical properties of the products obtained are in Tables 1 and 2.


1


2

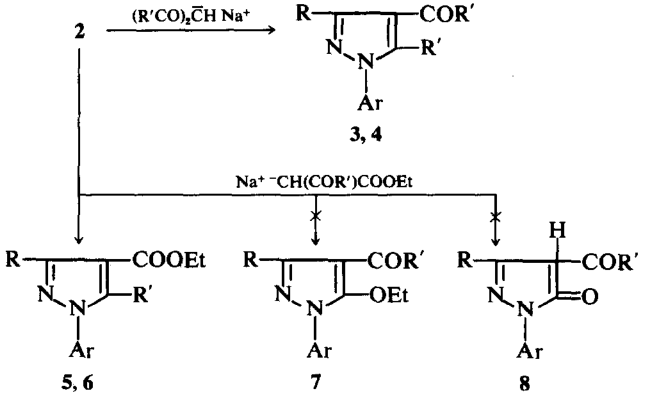
RESULTS AND DISCUSSION

Addition of hydrazidic bromide (**2a**) to a solution of the sodium salt of acetylacetone in EtOH at room temp gave readily one separable product (**3a**) which analysed for $C_{18}H_{15}N_3O_3$. The IR spectrum of **3a** exhibits an absorption band at 1675 cm^{-1} characteristic of conjugated acetyl carbonyl group[16] and another absorption at 1617 cm^{-1} corresponding to a C=N linkage of a pyrazole ring.[17] The NMR spectrum of **3a** in $CDCl_3$ reveals two singlets at δ 2·62 (3H) and 2·18 (3H) ppm. assignable to the CH_3CO and vinylic Me groups, respectively. Also, it shows a multiplet at δ 7·2–8·2 (9H) corresponding to the aromatic protons. Moreover, **3a** gave no colour with ethanolic $FeCl_3$ and did not couple with benzenediazonium ions. From these results, **3a** must be assigned the structure of 5-methyl-4-acetyl-3-phenyl-1-*p*-nitrophenylpyrazole. Its UV absorption spectrum in EtOH is also consistent with this structure. Other hydrazidic bromides **2b**, **c**, **f** and **h** reacted similarly with acetylacetone to give the corresponding pyrazole derivatives **3b**, **c**, **f** and **h**, respectively.

Reaction of **2a** with dibenzoylmethane gave, as sole isolable products, 5-phenyl-4-benzoyl-3-aryl-1-*p*-nitrophenylpyrazoles (**4a–e** and **h**); the elemental analyses being consistent with the assigned structures. The NMR spectra in $CDCl_3$ revealed in each case, only the usual aromatic proton multiplet signal at δ 7·3–8·4 ppm. The IR spectrum of each compound in the series **4** showed two characteristic absorption bands: one at 1649 cm^{-1} assignable to conjugated benzoyl carbonyl group and the second at 1620 cm^{-1} due to the C=N stretch.

Next, the reactions of the carbanions of β-keto esters with **2** were studied. This is of interest as such carbanions, unlike those of the β-diketones investigated, can undergo three possible modes of cyclization reactions with **2** to give **5**, **7** and/or **8** (Scheme 1).

2a with one equivalent of ethyl acetoacetate in EtOH in presence of NaOEt afforded a single product identified as 3-phenyl-5-methyl-1-*p*-nitrophenyl-4-carbethoxypyrazole (**5a**). In similar manner, other hydrazidic bromides (**2b–h**) reacted with ethyl acetoacetate and were converted to the corresponding pyrazole derivatives (**5b–h**) in good yields. The structure assignment of **5a–h** was based on their elemental analyses and physical properties. For example, **5a** gave no colour with ethanolic $FeCl_5$; did not couple with benzenediazonium salts in presence of either NaOAc or NaOH and was recovered unchanged when refluxed with ethanolic



3, R' = Me
4, R' = Ph

a R = Ph
b R = 2-ClC$_6$H$_4$
c R = 4-ClC$_6$H$_4$
d R = 4-CH$_3$C$_6$H$_4$
IR

5, R' = Me
6, R' = Ph

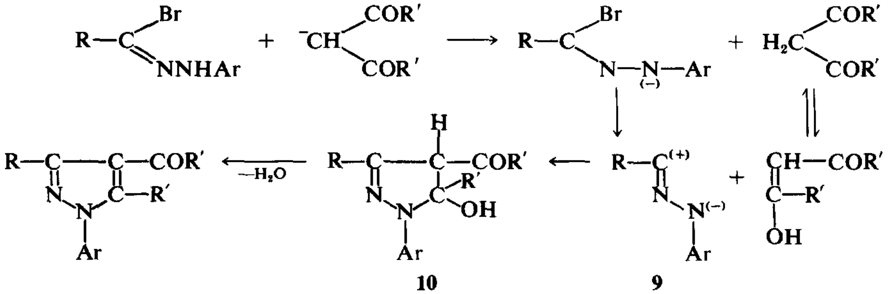
e R = 3-NO$_2$C$_6$H$_4$
f R = 4-NO$_2$C$_6$H$_4$
g R = 4-BrC$_6$H$_4$
h R = 2,4-Cl$_2$C$_6$H$_3$
3a

SCHEME 1

HCl. The IR spectrum of **5a** showed an α,β-unsaturated ester carbonyl stretching frequency at 1720 cm^{-1} and a C=N frequency at 1620 cm^{-1}.[16,17] Its NMR spectrum in CDCl$_3$ exhibited a multiplet at δ 7·5–8·3 (9H, aromatic), a quartet at δ 4·15 (2H, J 7 Hz, -$\underline{CH_2}$-CH$_3$), a triplet at δ 1·10 (3H, J 7 Hz, -CH$_2$-$\underline{CH_3}$) and a singlet at δ 2·70 (3H, vinylic Me at C-5) ppm. The chemical shift assignments were based on those of known compounds and integrated areas. The downward shift of the signal ascribed to the vinylic Me in **5a** is probably due to deshielding by the -COOEt group. These findings clearly indicate that structure **5** represents the products obtained from the reaction of **2** with ethyl acetoacetate. Both structures **7** and **8** are incompatible with the evidence.

Reactions of hydrazidic bromides (**2**) with ethyl benzoyl acetate seems to follow the same sequence and yield 1,3,5-triaryl-4-carbethoxypyrazoles (**6a–h**). The spectral data (IR, NMR and UV) of these products were in accordance with the assigned structures. **6a**, a typical example, showed a conjugated ester carbonyl stretching band at 1720 cm^{-1} and a pyrazole C=N stretch at 1620 cm^{-1} in its IR spectrum.[16,17] In addition, it showed only a multiplet signal at δ 7·3–8·3 ppm (14H, aromatic) and the usual ethyl pattern: a triplet at δ 0·90 (3H, J 7 Hz, -O-CH$_2$-CH$_3$) and a quartet at δ 4·03 ppm (2H, J 7 Hz, -O-CH$_2$-CH$_3$) in its NMR spectrum in CDCl$_3$. Like compounds of series **5**, the products **6a–h** gave no colour with FeCl$_3$ solution and were recovered unchanged upon acid treatment.

Inspection of the structures of the products obtained above suggests that the reaction described probably proceeds through the pathway represented in Scheme 2. The carbanion, acting as a base can react with **2** to form a nitrilimine dipole of type (**9**). Such 1,3-dipolar ions have been proposed for



SCHEME 2

the reactions of hydrazidic halides (**2**) conducted in the presence of strong bases.[10–12] The dipolar ion (**9**) then adds to the enol form of the β-diketone or β-keto ester to give (**10**). This addition reaction is analogous to the 1,3-dipolar cycloaddition of diphenylnitrilimine (**9**, R = Ar = Ph) to alkenes and alkynes to form 1,3-diphenyl-2-pyrazolines and 1,3-diphenylpyrazoles, respectively.[18–20] Subsequent loss of water from **10** would then give the corresponding pyrazole product. Such a mechanism would explain the formation of **5** and **6**, (rather than **7** or **8**) in the reaction of **2** with β-keto esters, since the acyl carbonyl rather than the ester carbonyl is involved in the enolization of β-keto esters as in 11.

R—C(OH):CHCOOR
11

The reaction of hydrazidic bromides and active methylene compounds appears to be an unequivocal method for the preparation of particular pyrazole isomers. It is an efficient and rapid experimental procedure which only necessitates readily available starting materials.

EXPERIMENTAL

Mps are uncorrected. IR spectra were recorded on a Beckman IR4 spectrophotometer, solids being examined as KBr discs. The NMR spectra were obtained in $CDCl_3$ on a Varian A60 NMR spectrometer with TMS as the internal standard. The UV spectra were measured on a Beckman DK spectrophotometer in EtOH.

The 4-nitrophenylhydrazones of benzaldehyde and its substituted derivatives were prepared in a rigorously similar manner by mixing equimolecular amounts of the hydrazine and aldehyde in ethanol-AcOH solution. The physical data obtained for the hydrazones prepared agreed with literature values.[21] 2,4-Dichlorobenzaldehyde 4-nitrophenylhydrazone (**Ih**), not yet reported, was obtained in 85% yield, m.p. 253°; (Calc. for $C_{13}H_9Cl_2N_3O_2$: C, 50·33; H, 2·92; Cl, 22·86. Found: C, 50·1; H, 2·9; Cl, 22·9%).

The hydrazidic bromides (**2a–h**) were prepared by the following general procedure. The hydrazone (0·03 mole) as a slurry in glacial AcOH (70 ml) at room temp was rapidly stirred while a solution of bromine (0·03 mole) in AcOH (20 ml) was added dropwise during 30 min. The hydrazidic bromides were collected after 5 h and water washed. Recrystallization was effected from AcOH. The hydrazidic bromide (**2h**), not yet reported, was obtained in 71% yield, m.p. 212, (Calc. for $C_{13}H_8BrCl_2N_3O_2$:

Table 1

Compound No.	m.p.	Yield, %	Found (%)				Formula	Calc. (%)				$\lambda^{EtOH}_{max.}$ (log ε)
			C	H	N	Cl		C	H	N	Cl	
	1-*p*-Nitrophenyl-3-aryl-4-acetyl-5-methylpyrazoles (3)											
3a	165	65	67·3	4·6	13·0		$C_{18}H_{15}N_3O_3$	67·3	4·7	13·1		300 (5·21); 255 (5·22)sh; 226 (5·41)
3b	179	63	60·6	3·7	11·8	10·0	$C_{18}H_{14}ClN_3O_3$	60·7	3·9	11·8	9·97	295 (5·26); 252 (5·20)sh;
3c	146	65	60·5	3·8	11·7	9·9	$C_{18}H_{14}ClN_3O_3$	60·7	3·9	11·8	9·97	300 (5·20); 255 (5·26)sh; 230 (5·42)
3f	163	72	59·1	3·6	15·1		$C_{18}H_{14}N_4O_5$	59·0	3·8	15·3		295 (5·41); 214 (5·45)sh
3h	148	60	55·5	3·2	10·8	18·2	$C_{18}H_{13}Cl_2N_3O_3$	55·4	3·3	10·8	18·1	295 (5·20); 250 (5·33)sh; 230 (5·46)sh
	1-*p*-Nitrophenyl-3-aryl-4-benzoyl-5-phenylpyrazoles (4)											
4a	151	70	75·4	4·2	9·3		$C_{28}H_{19}N_3O_3$	75·5	4·3	9·4		320 (5·27); 240 (5·60)
4c	175	68	70·0	3·7	8·7	7·5	$C_{28}H_{18}ClN_3O_3$	70·0	3·8	8·7	7·4	315 (5·24); 246 (5·97)
4d	159	75	75·7	4·6	9·2		$C_{29}H_{21}N_3O_3$	75·8	4·6	9·1		
4e	198·5	70	68·4	3·6	11·4		$C_{28}H_{18}N_4O_5$	68·6	3·7	11·4		310 (5·07); 242 (5·69)
4h	150	65	65·3	3·2	8·0	13·9	$C_{28}H_{17}Cl_2N_3O_3$	65·4	3·3	8·2	13·8	290 (5·28); 236 (5·52)

Table 2

Compound No.	m.p. °C	Yield, %	Found (%)				Formula	Calc. (%)				$\lambda^{EtOH}_{max.}$ (log ε)
			C	H	N	Cl		C	H	N	Cl	
	1-*p*-Nitrophenyl-3-aryl-4-carbethoxy-5-methylpyrazoles (5)											
5a	123	73	64·9	4·8	12·0		$C_{19}H_{17}N_3O_4$	65·0	4·9	11·9		300 (5·18); 250 (5·28)sh; 222 (5·46)
5b	145	72	59·1	4·1	10·8	9·3	$C_{19}H_{16}ClN_3O_4$	59·4	4·2	10·9	9·2	296 (5·25)
5c	174	70	59·6	4·1	10·9	9·3	$C_{19}H_{16}ClN_3O_4$	59·4	4·2	10·9	9·2	303 (5·26); 218 (5·54)
5d	139	68	65·7	5·3	11·3		$C_{20}H_{19}N_3O_4$	65·8	5·2	11·5		307 (5·15); 250 (5·23)sh; 222 (5·54)
5e	209	65	57·4	4·1	13·9		$C_{19}H_{16}N_4O_6$	57·6	4·0	14·1		295 (5·30); 250 (5·36)
5h	121	67	54·4	3·6	9·8	16·8	$C_{19}H_{15}Cl_2N_3O_4$	54·3	3·6	10·0	16·9	
	1-*p*-Nitrophenyl-3-aryl-4-carbethoxy-5-phenylpyrazoles (6)											
6a	119	75	69·6	4·5	10·0		$C_{24}H_{19}N_3O_4$	69·8	4·6	10·1		310 (5·17); 260 (5·23)sh; 227 (5·48)
6b	129	70	64·2	4·1	9·3	8·0	$C_{24}H_{18}ClN_3O_4$	64·5	4·1	9·4	7·9	302 (5·23)
6c	140	70	64·2	4·0	9·4	7·9	$C_{24}H_{18}ClN_3O_4$	64·5	4·1	9·4	7·9	
6d	119	73	70·3	4·9	9·6		$C_{25}H_{21}N_3O_4$	70·2	4·9	9·8		315 (5·22); 260 (5·32)sh; 230 (5·51)
6e	137	65	63·0	3·7	12·1		$C_{24}H_{18}N_4O_6$	62·9	3·9	12·2		
6f	170	65	63·0	3·8	12·1		$C_{24}H_{18}N_4O_6$	62·9	3·9	12·2		302 (5·42)
6g	138	70	58·5	3·5	8·3		$C_{24}H_{18}BrN_3O_4$	58·6	3·6	8·5		308 (5·21); 255 (5·42); 229 (5·52)
6h	148	75	59·6	3·5	8·7	14·8	$C_{24}H_{17}Cl_2N_3O_4$	59·8	3·5	8·7	14·7	

C, 40·1; H, 2·07; Br, 20·5; Cl, 18·2. Found: C, 40·2; H, 2·1; Br, 20·3; Cl, 18·1%). The mps of all other hydrazidic bromides (**2a–g**) agreed with literature values.[7–9]

Reaction of 2 with carbanions of β-diketones. General Method. To an ethanolic solution of NaOEt (prepared from Na metal (0·11 g, 0·005 g. atom) and 20 ml of absolute EtOH) was added 0·005 mole of the appropriate β-diketone. After stirring for 15 min at room temp, the hydrazidic bromide (**2**) (0·005 mole) was added and stirring continued for 6 h during which the hydrazidic bromide dissolved and a pale yellow solid precipitated. The latter was filtered, water washed and recrystallized from EtOH. The compounds (**3** and **4**) prepared together with their physical constants are listed in Table 1.

Ethyl 1,3,5-*trisubstituted pyrazole*-4-*carboxylates* (**5** and **6**). These were prepared by the same general procedure described above, using β-keto ester in place of β-diketone. Table 2 lists the compounds and their physical properties. All compounds (**3–6**) gave no colour with ethanolic $FeCl_3$.

Attempted hydrolysis of **5** *and* **6**. A solution of **5a** (0·001 mole) in 100 ml of absolute EtOH was saturated (while cooling in ice-bath) with HCl (3 h). The resulting mixture was refluxed for 2 h, cooled and filtered. Recrystallization gave 1·6 g (95%) of the starting **5a**; **6a** similarly treated, was also recovered unchanged.

REFERENCES

[1] F. D. Chattaway and A. J. Walker, *J. Chem. Soc.* 975 (1925)

[2] A. F. Hegarty and F. L. Scott, *J. Org. Chem.* **33**, 753 (1968)

[3] R. N. Butler and F. L. Scott, *J. Chem. Soc.* (C) 239 (1967)

[4] M. S. Gibson, *Tetrahedron* **18**, 1377 (1962)

[5] M. S. Gibson, *Ibid.* **18**, 1587 (1962)

[6] T. Bacchetti, *Gazz. Chim. Ital.* **91**, 866 (1961)

[7] J. B. Aylward and F. L. Scott, *J. Chem. Soc.* (B) 1080 (1969)

[8] A. F. Hegarty and F. L. Scott, *Ibid.* 1031 (1966)

[9] A. F. Hegarty and F. L. Scott, *Ibid.* 672 (1966).

[10] J. S. Clovis, A. Eckell, R. Huisgen and R. Sustmann, *Chem. Ber.* **100**, 60 (1967)

[11] R. Huisgen, *Bull. Soc. Chim. France* 3431 (1965); *Angew. Chem. Internat. Edn.* **2**, 565 (1963); *J. Org. Chem.* **33**, 2291 (1968)

[12] A. F. Hegarty, M. P. Cashman and F. L. Scott, *Chem. Comm.* **13**, 684 (1971)

[13] F. L. Scott and D. A. Cronin, *Tetrahedron Letters* 715 (1963)

[14] F. L. Scott and J. B. Aylward, *Ibid.* 841 (1965)

[15] F. L. Scott, M. P. Cashman and A. F. Hegarty, *J. Chem. Soc.* (B) 1607 (1971)

[16] C. Wijnberger and C. L. Habraken, *J. Hetero. Chem.* **6**, 545 (1969)

[17] R. Jones, A. J. Ryan, S. Sternhell and S. Wright, *Tetrahedron* **19**, 1497 (1963)

[18] R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Ibid.* **17**, 3 (1962)

[19] J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich and V. Weberndörfer, *Chem. Ber.* **100**, 1593 (1967)

[20] R. Huisgen, R. Sustmann and G. Wallbillich, *Ibid.* **100**, 1786 (1967)

[21] C. D. Hodgemann, *et al.*, *Tables for Identification of Organic Compounds*, Chemical Rubber Publishing Co., Cleveland, Ohio (1960)