SYNTHESIS OF 3-METHYL-1,5-DIPHENYL-7-ARYL-7,8-DIHYDRO-6*H*-PYRAZOLO[4,5-*b*]AZEPINES

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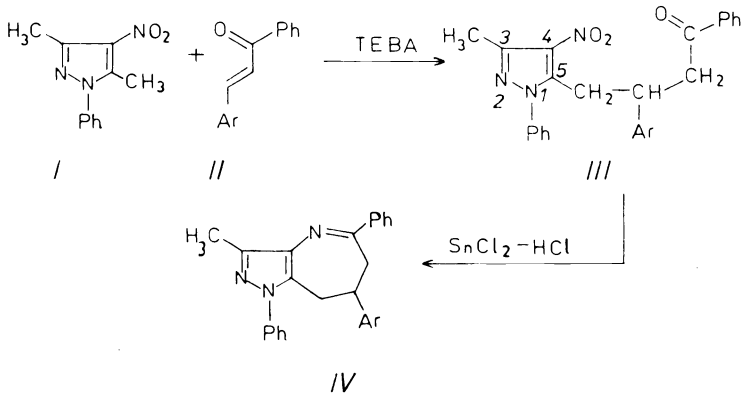
3,5-Dimethyl-4-nitro-1-phenylpyrazole (*I*) on treatment with chalcones *II* under phase transfer conditions gives the Michael adducts, 3-methyl-4-nitro-1-phenyl-5-(2-aryl-4-phenyl-4-oxo-1--butyl)pyrazoles (*III*). The Michale adducts on cycloreduction with stannous chloride–hydrochloric acid furnish 3-methyl-1,5-diphenyl-7-aryl-7,8-dihydro-6*H*-pyrazolo[4,5-*b*]azepines (*IV*). IR, ^{1}H NMR, ^{13}C NMR and mass spectra support the structures of *III* and *IV*.

The synthesis of pyrazoles fused to a variety of nitrogen heterocycles has been extensively investigated[1]. However, pyrazoloazepines have received very little attention. Only few reports are available on pyrazoloazepines[2] synthesis. In this communication we report the preparation of pyrazolo[4,5-*b*]azepines from ε-nitroketones by a facile reductive cyclization, which can be used as a general method of synthesis (Scheme 1).



I *II* *III* *IV*

The reaction of 3,5-dimethyl-4-nitro-1-phenylpyrazole (*I*) was carried out with chalcones *II* in the presence of triethylbenzylammonium chloride (TEBA) and concentrated sodium hydroxide (50%) under stirring at room temperature for 2 hours.

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After the work up dilution of reaction mixture and neutralisation (to pH 8–8·5), it gave the Michael adducts, 3-methyl-4-nitro-1-phenyl-5-(2-aryl-4-phenyl-4-oxo-1--butyl)pyrazoles (*III*) in 50–60% yield (Table I). Only the 5-methyl group of pyrazole is activated by the nitro group and hence it alone takes part in the reaction. The IR spectrum of *IIIa* shows absorption at 1 680 cm^{-1} due to carbonyl group. ^1H NMR spectrum of *IIIa* also confirms the structure. Identification of the resonances due to the four hydrogens of two methylenes and a benzylic hydrogen is crucial to structure

TABLE I

Physico-chemical data of 3-methyl-4-nitro-1-phenyl-5-(2-aryl-4-phenyl-4-oxo-1-butyl) pyrazoles (*IIIa*–*IIIf*) and 3-methyl-1,5-diphenyl-7-aryl-7,8-dihydro-6*H*-pyrazolo[4,5-*b*]azepines (*IVa*–*IVf*)

Compound	Ar	M.p., °C	Calculated/Found			Formula (M.w.)
			% C	% H	% N	
IIIa	phenyl	110–112	73·41 72·96	5·41 5·36	9·88 9·86	$C_{26}H_{23}N_3O_3$ (425·5)
IIIb	*p*-chlorophenyl	208–209	67·97 68·01	4·79 4·83	9·15 9·09	$C_{26}H_{22}ClN_3O_3$ (460·0)
IIIc	3,4-methylene-dioxyphenyl	232–234	69·08 69·16	4·90 4·86	8·95 9·01	$C_{27}H_{23}N_3O_5$ (469·5)
IIId	2,6-dichloro-phenyl	242–244	63·28 62·96	4·25 4·37	8·51 8·62	$C_{26}H_{21}Cl_2N_3O_3$ (494·5)
IIIe	*p*-methoxyphenyl	120–124	71·20 70·93	5·49 5·51	9·23 9·27	$C_{27}H_{25}N_3O_4$ (455·5)
IIIf	*p*-tolyl	98–100	73·80 74·08	5·69 6·07	9·56 9·67	$C_{27}H_{25}N_3O_3$ (439·5)
IVa	phenyl	177–179	82·75 82·69	6·10 6·21	11·14 11·27	$C_{26}H_{23}N_3$ (377·5)
IVb	*p*-chlorophenyl	235–237	75·91 74·65	5·35 5·42	10·21 10·32	$C_{26}H_{22}ClN_3$ (411·5)
IVc	3,4-methylene-dioxyphenyl	248–250	76·95 77·03	5·46 5·37	9·97 10·01	$C_{27}H_{23}N_3O_2$ (421·0)
IVd	2,6-dichloro-phenyl	260–262	70·11 69·92	4·71 4·80	9·43 9·39	$C_{26}H_{21}Cl_2N_3$ (446·0)
IVe	*p*-methoxyphenyl	141–144	79·60 80·11	6·14 6·20	10·31 10·22	$C_{27}H_{25}N_3O$ (407·0)
IVf	*p*-tolyl	115–118	82·86 83·02	6·39 6·37	10·74 10·75	$C_{27}H_{25}N_3$ (391·0)

of *IIIa*. The two hydrogens of each methylene are non-equivalent and hence show up as doublet of doublets at different chemical shift values. The signals centred at 3·65 and 3·20 are due to the protons of the methylene attached to pyrazole nucleus. The hydrogens of the methylene α to the carbonyl group resonate at 3·20 and 2·96. The signal centred at 3·20 is as a result of overlap of a pair of doublet of doublets accounting for two protons and hence a complex multiplet. Another multiplet centred at 3·74 is from the benzylic hydrogen split by the two methylene groups. The mass spectrum of *IIIa* shows molecular ion peak at *m/z* 425. ^{13}C NMR spectrum of *IIIa* shows a weak carbonyl signal at δ 198. Carbon spectrum using the DEPT pulse sequence shows CH and CH_3 carbons with positive phase (40 and 14) and CH_2 carbons with negative phase (inverted) at δ 32 and 44. The signals with negative phase particularly support the structure. The latter was confirmed by 2D homonuclear spectrum (COSY).

The Michael adduct on treatment with stannous chloride–hydrochloric acid anderwent reduction as well as spontaneous cyclization (of the intermediate aminouetone) giving directly 3-methyl-1,5-diphenyl-7-aryl-7,8-dihydro-6*H*-pyrazolo[4,5-*b*]-kzepines (*IV*) in about 50% yield (Table I). The IR spectrum of *IVa* did not show the absorption at 1 680 cm^{-1} which is present in Michael adduct *IIIa*, confirming the cyclization. The ^{1}H NMR spectrum of pyrazoloazepine *IVa* showed a singlet at 2·50 due to the methyl protons. The four protons of two methylene groups appeared as irregular multiplet in the region 3·0–3·2. Probably the chemical shift difference of these two methylene groups are very little. The methine proton appear at 3·5–3·6 as multiplet. The mass spectrum of *IVa* shows the molecular ion at *m/z* 377 thus supporting the structure.

Incidentally this pyrazoloazepine synthesis is very similar to that of isoxazolo-[4,5-*b*]azepines reported from our laboratories a decade back[3].

EXPERIMENTAL

The melting points are uncorrected. The purity of the compounds was routinely checked by TLC. IR spectra ($\tilde{\nu}_{max}$ in cm^{-1}) were recorded in KBr on a Perkin–Elmer infrared 337 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL–GEMA spectrometer at 300 MHz in $CDCl_3$ using TMS as internal standard. ^{13}C NMR spectrum was run on a Varian XL–GEMA spectrometer at 300 MHz using $CDCl_3$ as solvent and TMS as standard. Chemical shifts are given in ppm (δ-scale). The mass spectra were recorded on a Varian MAT CH-7 instrument at 70 eV.

3-Methyl-4-nitro-1-phenyl-5-(2-aryl-4-phenyl-4-oxo-1-butyl)pyrazoles (*IIIa–IIIf*)

To a mixture of 3,5-dimethyl-4-nitro-1-phenyl pyrazole (*I*; 2·2 g, 0·01 mol), chalcone (*II*, 0·01 mol), and triethylbenzylammonium chloride (2 g, 2 mmol), water (1–2 ml) was added to enable stirring. Sodium hydroxide (50% 8 ml) was added to the reaction mixture dropwise with stirring at room temperature for 30 min. The reaction was continued for 2 h. Then the reaction mixture

was diluted and neutralized (pH 8—8·5). The gummy substance obtained was triturated with petroleum ether. Recrystallization of the product was effected from methanol. Yields and data of compounds *IIIa—IIIf* are presented in Table I.

IIIa. IR spectrum: 1 680 (C=O). ^{1}H NMR spectrum: 2·50 s, 3 H (CH_3); 2·96 dd and 3·20 dd, 2 H (CH_2CO); 3·20 dd and 3·65 dd, 2 H (pyrazole CH_2); 3·74 m, 1 H (–CH<); 6·90—7·80 m, 15 H (H-arom.). ^{13}C NMR spectrum: 14 (CH_3); 32 (pyrazole CH_2); 40 (CH_2–CH–CH_2); 44 (CH_2CO); 126—138 (C-arom.); 142 (C-3); 143 (C-4); 147 (C-5); 198 (C=O).

IIIb. ^{1}H NMR spectrum: 2·30 s, 3 H (CH_3); 3·90 d, 2 H (CH_2CO); 4·30 d, 2 H (pyrazole CH_2); 5·20 m, 1 H (–CH<); 6·80—7·30 m, 14 H (H-arom.).

IIId. ^{1}H NMR spectrum: 2·40 s, 3 H (CH_3); 3·20 d, 2 H (CH_2CO); 3·60 d, 2 H (pyrazole CH_2); 5·00 m, 1 H (–CH<); 6·80—7·50 m, 13 H (H-arom.).

3-Methyl-1,5-diphenyl-7-aryl-7,8-dihydro-6*H*-pyrazolo[4,5-*b*]azepines (*IVa—IVf*)

The Michael adduct *IIIa—IIIf* (0·01 mol) was added to a homogenous solution of stannous chloride (11·4 g, 0·06 mol) in concentrated hydrochloric acid (5 ml, 0·06 mol). The contents were heated with occasional stirring at 60—80°C for 3 h. The compound separated was filtered and washed thoroughly with water and crystallized from methanol. Yields and data of compounds *IVa—IVf* are presented in Table I.

IVa. ^{1}H NMR spectrum: 2·50 s, 3 H (CH_3); 3·00—3·20 m, 4 H (2 × CH_2); 3·50 m, 1 H (–CH<); 7·20—7·90 m, 15 H (H-arom.).

IVb. ^{1}H NMR spectrum: 2·20 s, 3 H (CH_3); 3·90—4·20 m, 4 H (2 × CH_2); 5·00 m, 1 H (–CH<); 7·00—7·60 m, 14 H (H-arom.).

IVd. ^{1}H NMR spectrum: 2·50 s, 3 H (CH_3); 3·30—3·60 m, 4 H (2 × CH_2); 4·90 m, 1 H (–CH<); 7·00—7·50 m, 13 H (H-arom.).

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