A GENERAL METHOD OF PREPARATION OF N-DIFORMYLMETHYL-AZOLES AND CYCLOIMONIUM DIFORMYL METHYLIDES

Vladimír KRÁL[a], Viktor Vladimirovich SEMENOV[b], Mikhail Ivanovich KANISHCHEV[b], Zdeněk ARNOLD[a], Svyatoslav Arkadievich SHEVELEV[b] and Albert Aleksandrovich FAINZILBERG[b]

[a] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6, Czechoslovakia and*
[b] *N. D. Zelinsky Institute of Organic Chemistry, Academy of Sciences of the U.S.S.R., Moscow B-334, U.S.S.R.*

Received November 25th, 1987
Accepted December 21st, 1987

Formylation of easily accessible heteroarylacetic acids (R—CH_2COOH, R = imidazole, pyrazole, tetrazole, pyridine) afforded in high yields the corresponding trimethinium salts R—C(=CH—$N(CH_3)_2$)CH=$N(CH_3)_2$)$^{n+}$ nX^- which on alkaline hydrolysis were converted into N-diformylmethylazoles R—C(CHO)=CH—OH. Their quaternization gave cycloimonium diformyl methylides.

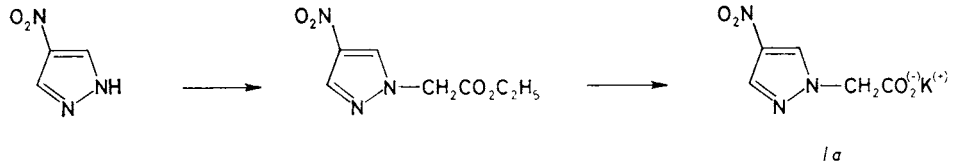
Malonaldehyde and its derivatives represent frequently used synthons for the synthesis of heterocyclic compounds and therefore a general method leading to substituted malonaldehydes is very desirable. For a long time, our attention has been focussed on amino derivatives of malonaldehyde. An attempt to prepare these compounds by reaction of bromomalonaldehyde with secondary amines is described[1] but this, however, leads to diaminoethylenes.

We have published[2] a general approach to amino derivatives of malonaldehydes consisting in formylation of glycine (or substituted glycines) and subsequent hydrolysis of the obtained trimethinium salt under formation of aminomalonaldehyde, followed by alkylation[3]. Aminomalonaldehyde also represents a very useful synthon for synthesis of a new series of stabilized ammonium ylides – trimethylammoniodiformyl methylide[4] and N,N-dimethyl-N-alkylammoniodiformyl methylides[5].

A series of malonaldehyde derivatives of the type R—C(CHO)=CH—OH, where R is a nitrogen-containing heterocyclic system, has been obtained by formylation of an active methylene or methyl groups: thus, e.g. under conditions of Vilsmeier reaction, 4-methylpyridine undergoes diformylation at the methyl group, giving rise to the corresponding malonaldehyde derivative[6].

With the aim to obtain N-diformylmethylazoles and subsequently cycloimonium diformyl methylides we investigated the formylation of heteroarylacetic acids[7].

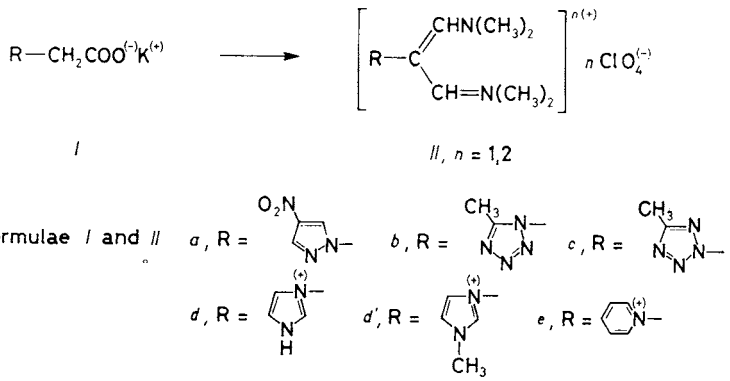
N-Heteroarylacetic acids were obtained by alkylation of nitrogen heterocyclic compounds with bromoacetic acid or its alkyl ester. On the preparative scale, it was better to use the ester because of easier isolation of the product. The esters were readily hydrolyzed with equimolar amount of potassium hydroxide in methanol to give salts of the corresponding heteroarylacetic acid *I*. In this way we prepared e.g. potassium salt of 4-nitropyrazolyl-1-acetic acid (Scheme 1). Formylation of N-heteroarylacetic acids (or their salts prepared according to Scheme 1) under conditions



Ia

SCHEME 1

of Vilsmeier reaction gave trimethinium salts *II*, well isolable as the perchlorates (Scheme 2). In cases where R = imidazole (*IId*) and R = pyridine (*IIe*), the salts contain a bivalent cation. Under the reaction conditions (80–90°C), the reaction course can be qualitatively monitored by CO_2 evolution (in the reaction two formyl groups are introduced with simultaneous decarboxylation). Quantitative kinetic



I *II*, *n* = 1,2

In formulae *I* and *II* *a*, R = *b*, R = *c*, R = *d*, R = *d'*, R = *e*, R =

SCHEME 2

study is possible thanks to the strong maximum at 300–305 nm (ε 35 000–43 000) in the UV spectrum of the arising trimethinium salts. Structure of the trimethinium salts was confirmed by elemental analysis, NMR and UV spectra (Table I). The

TABLE I

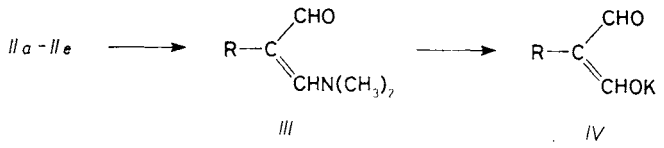
Data for trimethinium salts *IIa*—*IIe*

Compound	Reaction time, h	Yield %	M.p., °C (ethanol)	λ_{max}, nm (ε)[a]	^{1}H NMR[b]	Formula (mol. w.)	Calculated/found			
							% C	% H	% N	% Cl
IIa	4·2	87	283—285	302 (41 500)	2·38 s, 3·31 s ($N(CH_3)_2$); 7·98 s (CH=); 8·55, 9·03 (pyrazole)	$C_{10}H_{16}ClN_5O_6$ (337·7)	35·56 35·29	4·74 4·69	20·74 20·53	10·52 10·99
IIb	4·5—5	54	215—217 (H_2O)	300 (43 000)	2·14 s, 3·30 s ($N(CH_3)_2$); 2·53 s (CH_3); 8·04 s (CH=)	$C_9H_{17}ClN_6O_4$ (308·8)	35·00 34·89	5·51 5·47	27·22 27·03	11·51 11·32
IIc	4·5—5	76	242—243	301·2 (43 500)	2·33 s, 3·37 s ($N(CH_3)_2$); 2·58 s (CH_3); 7·88 s (HC=)	$C_9H_{17}ClN_6O_4$ (308·8)	35·00 34·82	5·51 5·46	27·22 26·82	11·51 11·75
IId	5	99	162—163	306·2 (41 000)	2·57 s, 3·37 s ($N(CH_3)_2$); 7·75 m (HC=, H-4, H-5); 9·07 (H-2)	$C_{10}H_{18}Cl_2N_4O_8$ (393·2)	30·55 30·51	4·61 4·57	14·25 14·21	18·03 18·10
IIe	4·5	53	185—186	305 (35 000) 270 (9 700)	2·50 bs, 3·43 s ($N(CH_3)_2$); 7·85 s (HC=); 8·23—9·15 (pyridine)	$C_{12}H_{19}Cl_2N_3O_8$ (404·2)	35·66 35·58	4·74 4·72	10·40 10·35	17·54 17·27

[a] In water; [b] in deuterium oxide.

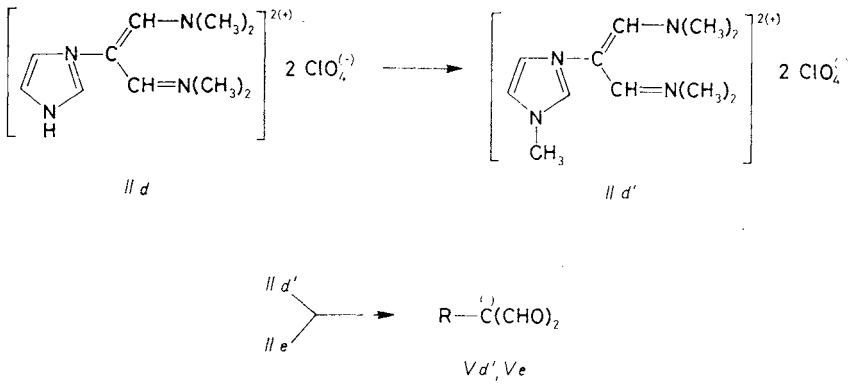
salts *II* are stable compounds that crystallize well from ethanol or water. The yields of the formylation reaction range between 60 and 70%.

Further reaction step on the way towards the desired products, basic hydrolysis of the trimethinium salts, was performed under various conditions and afforded not only the final malonaldehyde derivative but also the first hydrolysis product – the corresponding acrolein derivative *III* (Scheme 3).



SCHEME 3

Hydrolysis with one equivalent of base or with a solution of potassium hydrogen carbonate at temperatures below 40°C led to acrylaldehydes *III* detectable by an absorption at 280 nm in the UV spectra of the reaction mixture. In the cases of 4-nitropyrazole and 5-methyl-1-tetrazole the acrylaldehydes *IIIa* and *IIIb* were isolated and characterized. Reaction with an excess of potassium hydroxide or with potassium hydrogen carbonate under more vigorous conditions afforded potassium salts of N-diformylmethylazoles *IV*, stable compounds whose characteristics are given in Table II. Treatment with mineral acids furnished the corresponding derivatives of malonaldehyde.



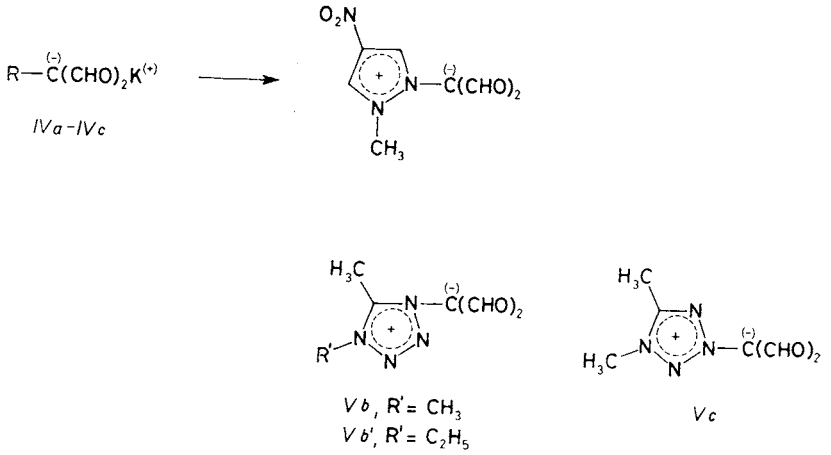
SCHEME 4

Hydrolysis of trimethinium salts *IId'* and *IIe*, which bear a positive charge on the nitrogen heterocyclic ring, afforded the first representatives of the hitherto unknown

cycloimonium diformyl methylides (Scheme 4). The hydrolysis has to be performed with potassium hydroxide or hydrogen carbonate because the corresponding sodium derivatives form very stable equimolecular complexes with ammonium ylides, as described already previously[4,5]. The prepared compounds may be classed among the group of stabilized ylides because the negative charge of the ylide carbon atom is delocalized by the two formyl groups.

Trimethinium salts with positively charged heterocylic ring cannot be hydrolyzed in strongly acidic media because of danger of ring fission.

The cycloimonium diformyl methylides can be prepared by two methods: either by the above-mentioned alkylation of the heterocycle in trimethinium salts (Scheme 4) or by quaternization of the heterocycle in N-diformylmethylazoles. Compounds containing less basic rings require either vigorous conditions (high pressure and temperature) or better very efficient alkylation reagents (methyl fluorosulfonate or triethyloxonio tetrafluoroborate) (Scheme 5).



SCHEME 5

The prepared cycloimonium diformyl methylides *V* are yellowish high-melting crystalline substances, soluble (except the not very stable tetrazole derivatives *Vb* and *Vb'*) in polar solvents and water. They can be crystallized from benzene or sublimed. The new compounds were characterized by elemental analysis and UV, IR and ^{1}H NMR spectra (Table II). In high-resolution mass spectra we determined molecular ions (elemental composition), fragments [M – CO], [M – CHO], [M – CO – OH] and ions of the corresponding heterocycles. The UV spectra of the obtained ylides exhibit a strong maximum at about 260 nm (ε 23 000–27 000), characteristic of a negatively charged malonaldehyde fragment bonded to the nitrogen atom[4,5]. The prepared compounds serve as a very valuable starting material for preparation of bicyclic systems containing an N—C bond between the heterocycles.

TABLE II

Data for N-diformylmethylazoles and cycloimonium diformylmethylides

Compound	Yield %	M.p., °C (C_6H_6)	Formula (mol. w.)	λ_{max}, nm (ε)[a]	^{1}H NMR[b]	Calculated/found		
						% C	% H	% N
IIIa	90	193–195	$C_8H_{10}N_4O_3$	280	3·37 s ($N(CH_3)_2$); 7·57 s (CH=);	45·71	4·79	26·66
			(210·2)	(36 500)	8·88 s (CHO); 8·35, 8·75 (pyrazole)	45·58	4·70	26·13
IIIb	95	101–102	$C_7H_{11}N_5O$	280·5	2·44 s (CH_3); 3·25 s ($N(CH_3)_2$);	46·39	6·12	38·65
			(181·2)	(38 000)	7·29 s (CH=); 9·04 s (CHO)	46·21	6·07	38·46
IVa	92	238–239	$C_6H_4KN_3O_4$	263	8·6 s (CHO); 8·16, 8·36 (pyrazole)	32·47	1·82	19·00
			(221·2)	(25 800)		32·41	1·90	18·75
IVb	90	decomp.	$C_5H_5KN_4O_2$	260·4	2·38 s (CH_3); 8·86 s (CHO)	31·24	2·62	29·15
			(192·2)	(26 300)		31·01	2·56	28·95
IVc	85	decomp.	$C_5H_5KN_4O_2$	259·5	2·55 s (CH_3); 8·84 s (CHO)	31·24	2·62	29·15
			(192·2)	(26 400)		31·08	2·59	29·03

Va	63	oil	$C_7H_7N_3O_4$ (197·2)	261·5 (21 400)	3·98 s (NCH_3); 8·98 bs (CHO); 9·47, 9·60 (CH, pyrazole)	42·64 42·51	3·58 3·59	21·32 21·12
Vb	80	oil	$C_6H_8N_4O_2$ (168·2)	258		42·85 42·58	4·79 4·58	33·32 33·02
Vc	64	202—203	$C_6H_8N_4O_2$ (168·2)	257 (23 000) 320·5 (2 300)	2·80 s (CCH_3); 4·28 s (NCH_3); 9·04 bs (CHO)	42·85 42·70	4·79 4·68	33·32 33·15
Vd'	65	176—177	$C_7H_8N_2O_2$ (152·2)	263·2 (26 800)	3·90 s (NCH_3); 8·78 bs (CHO); 7·08 t, 8·56 t, 9·64 q (imidazole)	55·25 55·17	5·30 5·19	18·42 18·51
Ve	85	208—209	$C_8H_7NO_2$ (149·1)	261 (24 400) 246 (16 900)	8·91 bs (CHO); 7·56—9·03 m (pyridine)	64·42 64·30	4·73 4·75	9·39 9·21

[a] In water; [b] in deuterium oxide.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Analytical samples were crystallized and dried over phosphorus pentoxide at 25°C/27 Pa for 24 h. ^{1}H NMR spectra were taken on a Varian XL 200 (200 MHz) and a Tesla BS 467 (60 MHz) instrument in deuteriochloroform and deuterium oxide with tetramethylsilane and sodium 2,2-dimethyl-2-silapentane-5-sulfonate, respectively, as internal standards. IR spectra were obtained with a Zeiss UR 20, UV spectra with a Unicam SP 8 000 instrument.

Potassium 4-Nitro-1-pyrazolylacetate (*Ia*)

Potassium hydroxide (2·13 g; 38 mmol) in water (5 ml) was added to a solution of 4-nitropyrazole (4·3 g; 38 mmol) in acetone (40 ml) at 20°C. After stirring for 5 min, ethyl bromoacetate (4·3 ml; 38 mmol) in acetone (10 ml) was added. The mixture was stirred for 15 h, potassium bromide was filtered off and the solvent was evaporated to give 6·73 g (89%) of ethyl 4-nitro-1-pyrazolylacetate; m.p. 47–48°C (cyclohexane) (reported[8] m.p. 46–46·5°C).

The thus obtained ester (5 g; 25 mmol) in ethanol (10 ml) was mixed with potassium hydroxide (1·4 g; 25 mmol) in ethanol (10 ml) at 20°C. After stirring for 1 h the salt was collected on filter, washed with ether and dried. Yield 4·6 g (95%). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 4·55 s (CH_2); 8·13 s, 1 H; 8·70 s, 1 H.

Salts of other heteroarylacetic acids were obtained analogously as described in ref.[9]. The salt *Ie* was described as its complex with hydrogen chloride obtained from equimolar amounts of pyridine and chloroacetic acid[10]. The hydrobromide was prepared analogously from bromoacetic acid and was used in the formylation reaction without further purification.

General Preparation of Trimethinium Perchlorates *II*

The formylation reagent was prepared by mixing phosphorus oxychloride (8·19 ml; 0·09 mol) with dimethylformamide (16·5 ml; 0·21 mol) at 0°C and stirring at room temperature for 30 min. The N-heteroarylacetic acid (or its salt) (0·03 mol) was added to the thus-prepared reagent. The mixture was heated to 80°C for 4–5 h (Table I), cooled to −40°C and diluted with pre-cooled ethanol (100 ml). The obtained solution was stirred with charcoal at room temperature for 10–15 min and filtered through Celite. A solution of 70% perchloric acid (15 ml; 0·1 mol) in ethanol (30 ml) was added to the filtrate and the mixture was set aside at −15°C to 0°C overnight. The yellow crystals of the trimethinium salt *II* were collected, washed with ether and dried in a desiccator.

Potassium Salts of N-Diformylmethylazoles *IVa–IVc*

To a suspension of the trimethinium salt *IIa–IIc* (3 mmol) in ethanol (10 ml) was added ethanolic 1M-KOH (3 ml), the mixture was stirred for 1 h and the precipitated potassium perchlorate was filtered off. From these filtrates aldehydes *IIIa* and *IIIb* were isolated.

The obtained solution of the aldehyde *IIIa–IIIc* was concentrated to 3–5 ml, mixed with 1M-KOH (10 ml) and set aside in a refrigerator overnight. Crystals of the product (*IVa–IVc*) were washed with cold ethanol, ether and dried in a desiccator over potassium hydroxide.

Preparation of Acrylaldehydes *IIIa–IIIb*

Potassium hydrogen carbonate (40 mmol) was added to a solution of *IIa* or *IIb* (2 mmol) in water (20 ml). The mixture was heated to 60°C for 2 h, taken down and the residue was extracted with

acetonitrile. The extract was stirred with charcoal, dried over magnesium sulfate and the solvent was evaporated to afford acrylaldehydes *IIIa* and *IIIb* in 90—95% yield.

Pyridiniumdiformyl Methylide (*Ve*)

A solution of trimethinium salt *IIe* (2 g) and potassium hydrogen carbonate (4 g) in water (20 ml) was heated to 80°C for 1·5 h. The mixture was taken down and the dry residue was extracted with chloroform (3 × 40 ml). The chloroform extract was stirred with charcoal and magnesium sulfate, filtered and concentrated to 5 ml. Ether (10 ml) was added and the precipitated product was filtered, washed with ether and dried in vacuo over phosphorus pentoxide. Yield 0·63 g (85%) of compound *Ve*.

Preparation of Cycloimonium Diformyl Methylides *Va*—*Vc* from N-Diformylmethylazoles *IVa*—*IVc*

Methyl fluorosulfate or triethyloxonio tetrafluoroborate (3 mmol) was added at room temperature during 1 h to a suspension of potassium salt of N-diformylmethylazole (3 mmol) in anhydrous acetonitrile. Ethanol (3 ml) was added, followed after 10 min with potassium hydrogen carbonate (1 g) and water (0·1 ml). After stirring for 45 min at room temperature, the solvent was evaporated and the dry residue was extracted with chloroform. The chloroform extract was dried over magnesium sulfate and filtered with charcoal. Evaporation of the solvent gave the ylides *Va*—*Vc*.

3-Methylimidazoliniumdiformyl Methylide (*Vd*)

A solution of trimethinium salt *IId* (1 g) in water (10 ml) was adjusted to pH 8—9 with potassium hydrogen carbonate (2 g). Dimethyl sulfate (0·7 ml) was added, the mixture was stirred at room temperature for 3 h and left to stand overnight. The hydrolysis of *IId* was performed by addition of potassium hydrogen carbonate (2 g) to the reaction mixture, heating to 80°C for 3 h, evaporation to dryness and isolation of *Vd'* in the same manner as described for *Ve*. Yield 0·25 g (65%).

4-Nitropyrazolylmalonaldehyde

Methanolic hydrogen chloride (20%; 20 ml) was added to a suspension of *IVa* (4·42 g; 20 mmol) in chloroform (50 ml) and the mixture was stirred at room temperature for 1 h. The precipitated potassium chloride was filtered and the solvent was evaporated to give 3·6 g (99%) of the product, m.p. 142°C.

REFERENCES

1. Duhamel L., Duhamel P., Truxillo V.: C. R. Acad. Sci., Ser C *275*, 225 (1972).
2. Arnold Z., Šauliová J., Krchňák V.: Collect. Czech. Chem. Commun. *38*, 2633 (1973).
3. Svoboda M., Král V., Arnold Z.: Collect. Czech. Chem. Commun. *42*, 1027 (1977).
4. Král V., Arnold Z.: Collect. Czech. Chem. Commun. *42*, 3455 (1977).
5. Svoboda M., Synáčková M., Samek Z., Fiedler P., Arnold Z.: Collect. Czech. Chem. Commun. *43*, 1261 (1978).
6. Arnold Z.: Collect. Czech. Chem. Commun. *28*, 863 (1963).
7. Král V., Arnold Z., Semenov V. V., Shevelov S. A., Fainzilberg V. V.: Izv. Akad. Nauk SSSR, Ser. Khim. *1983*, 955.

8. Simonenko L. S., Korsakova I. C., Novikov S. S.: Izv. Akad. Nauk SSSR, Ser. Khim. *1972*, 2332.
9. Raap R., Howard J.: Can. J. Chem. *47*, 813 (1969).
10. Bapat J., Epstain J., Katritzky A.: J. Chem. Soc., Perkin Trans. 1, *1977*, 1962.

Translated by M. Tichý.