The Use of α-(Aryl)-4-morpholineacetonitriles (Masked Acyl Anion Equivalents) in 1,4-Additions to α,β-Unsaturated Esters and Nitriles. A Versatile Synthetic Route to 6-Aryl-3(2*H*)pyridazinones

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The use of α-(substituted-phenyl)-4-morpholineacetonitriles in 1,4-additions to ethyl acrylate, ethyl crotonate, methyl α-methylacrylate, acrylonitrile, methylacrylonitrile, crotononitrile and cinnamonitrile was studied. A convenient route to 6-aryl-4,5-dihydro-3(2*H*)pyridazinones from aryl aldehydes and heterocyclic aldehydes was developed.

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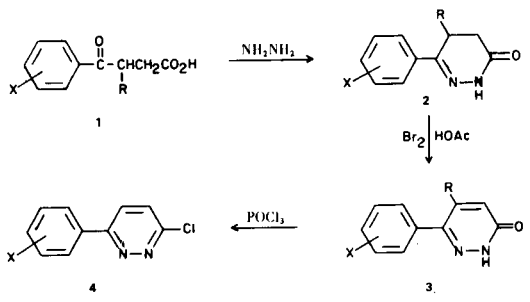
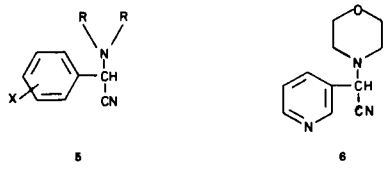
The object of this work was the preparation of 6-aryl-3(2*H*)pyridazinones (**3**) and 3-chloro-6-arylpyridazines (**4**). 3-Chloro-6-phenylpyridazines are generally synthesized from 3-(benzoyl)-3-alkanoic acids as shown in Scheme A. A general synthesis of 3-(substituted-benzoyl)-3-substituted alkanoic acids has been published by McEvoy and Allen (1) and a variety of 6-substituted phenyl-4,5-dihydro-3(2*H*)pyridazinones were prepared by McEvoy and Allen (2) and by Curran and Ross (3) as a class of compounds with potent hypotensive activity. 6-Phenyl-4,5-dihydro-3(2*H*)pyridazinones (**2**) are dehydrogenated by bromine (*via* bromination-dehydrobromination) in acetic acid to give 6-phenyl-3(2*H*)pyridazinones (**3**) (see Table V). Subsequent reaction of **3** with phosphorus oxychloride then affords the desired 3-chloro-6-phenylpyridazines (**4**) (see Table VI).

Scheme A



Another route to 3-(aroyl)propionic acids was sought in order to shorten the synthetic steps required for the preparation of intermediates **1**. In addition a versatile synthetic route which would give diverse substituted phenyl derivatives was desired as well as a route to 3-(heteroaroyl)propionic acids.

Recently Stetter has studied the addition of aryl aldehydes to α,β-unsaturated esters and nitriles (4). The anions from the intermediate cyanohydrins serve as masked acyl anion equivalents and the versatility of such anions in 1,4-additions has been reviewed by Stetter (5,6). The use of anions from *O*-alkylated cyanohydrins (7,8) and anions from *O*-silylated cyanohydrins (9) in the synthesis of ketones has been reported. Related masked acyl anion equivalents are those derived from α-(dialkylamino)acetonitriles (**5**) (10). Leete (11) first showed the utility of



α-morpholinoacetonitrile (**6**) in 1,4-additions to acrylonitrile; however, the general utility of this type of reaction in 1,4-additions has not been demonstrated.

We have used the α-(aryl)-4-morpholineacetonitriles derived from aryl aldehydes, substituted benzaldehydes and heterocyclic aldehydes to synthesize diverse 3-(aroyl), 3-(heteroaroyl) and 3-(substituted-benzoyl)propionic acids and esters. The literature procedure (11) was modified (12) to avoid the use of perchloric acid in the preparation of the α-(substituted-phenyl)-4-morpholineacetonitriles (**8**) (see Tables II and III). The availability of aryl aldehydes, diverse substituted benzaldehydes and heterocyclic aldehydes makes the synthesis of the intermediates of type **12** convenient and versatile. The intermediates **12**

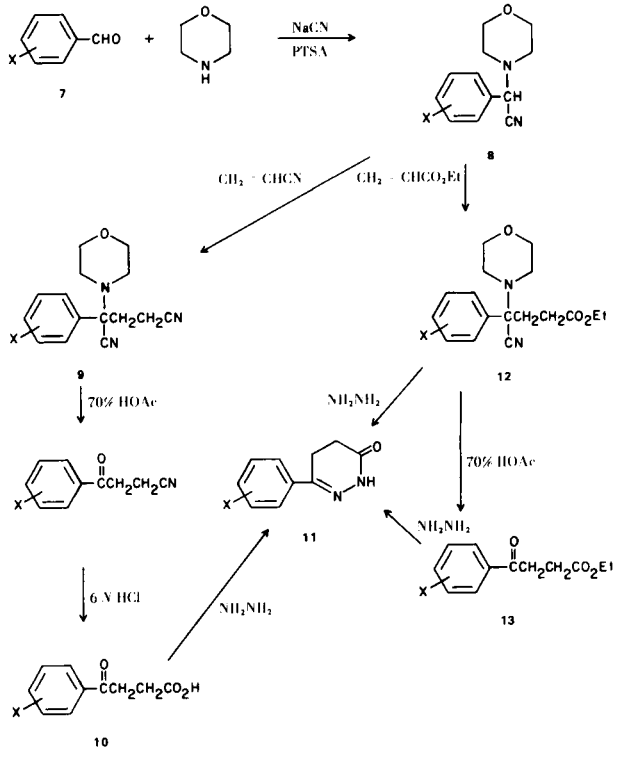


Table I

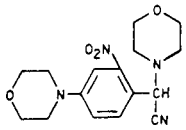
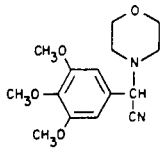
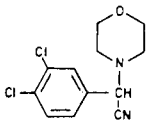
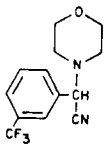
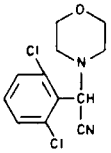
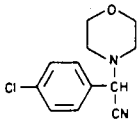
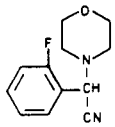
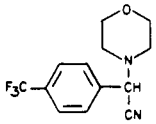
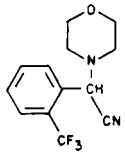
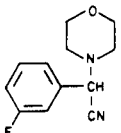
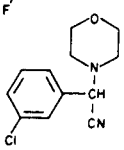
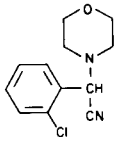
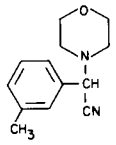
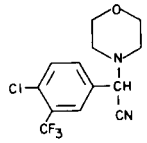
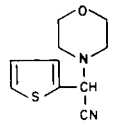
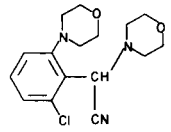
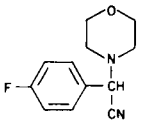
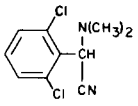
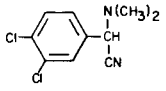
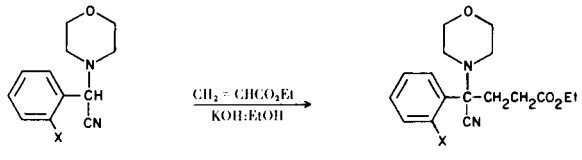
Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula		Analysis Calcd.	Found
	131-133	benzene-petroleum ether	99	A	$C_{16}H_{20}N_4O_4$	C H N	57.8 6.1 16.9	58.1 6.0 16.9
	137-139	benzene-petroleum ether	45	A	$C_{15}H_{20}N_2O_4$	C H N	61.6 6.9 9.6	61.7 6.9 9.5
	62-64	benzene-petroleum ether	78	A	$C_{12}H_{12}Cl_2N_2O$	C H N Cl	53.2 4.5 10.3 26.2	55.3 4.3 9.7 22.9
	yellow oil		95	A	$C_{13}H_{13}F_3N_2O$	C H N F	57.8 4.9 10.4 21.1	57.7 4.8 10.0 21.4
	64-67	petroleum ether	77	A	$C_{12}H_{12}Cl_2N_2O$	C H N Cl	53.2 4.5 10.3 26.2	52.9 4.2 10.1 26.9
	70-71	chloroform-hexane	72	A	$C_{12}H_{13}ClN_2O$	C H N Cl	60.9 5.5 11.8 15.0	60.9 5.5 11.8 15.1
	yellow oil		99	A	$C_{12}H_{13}FN_2O$	C H N F	65.4 6.0 12.7 8.6	65.2 6.1 12.5 8.7
	89-90	hexane	75	A	$C_{13}H_{13}F_3N_2O$	C H N F	57.8 4.9 10.4 21.1	57.8 4.8 10.3 21.2
	oil		93	A	$C_{13}H_{13}F_3N_2O$	C H N	57.8 4.9 10.4	57.7 4.7 10.5
	74-75	dichloromethane-hexane	66	A	$C_{12}H_{13}FN_2O$	C H N F	65.4 6.0 12.7 8.6	65.6 5.9 13.0 8.6
	72-73	chloroform-hexane	72	A	$C_{12}H_{13}ClN_2O$	C H N Cl	60.9 5.5 11.8 15.0	60.9 5.5 11.9 15.2

Table I (continued)

Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula		Analysis Calcd.	Found
	40-42	chloroform-hexane	65	A	$C_{12}H_{13}ClN_2O$	C H N Cl	60.9 5.5 11.8 15.0	60.8 5.5 11.7 14.9
	59-60	chloroform-hexane	65	A	$C_{13}H_{16}N_2O$	C H N	72.2 7.5 13.0	72.4 7.2 13.0
	73-74	dichloromethane-hexane	69	A	$C_{13}H_{12}ClF_3N_2O$	C H N Cl F	51.2 4.0 9.2 11.6 18.7	51.4 4.1 9.3 11.6 19.0
	78-79	dichloromethane-hexane	90	A	$C_{10}H_{12}N_2OS$	C H N S	57.7 5.8 13.5 15.4	57.5 5.6 13.4 15.4
	138-140	dichloromethane-hexane	40	A	$C_{16}H_{20}ClN_3O_2$	C H N Cl	59.7 6.3 13.1 11.0	60.0 6.3 13.0 11.0
	60-63	dichloromethane-hexane	82	A	$C_{12}H_{13}FN_2O$	C H N F	65.4 6.0 12.7 8.6	65.7 6.3 12.6 8.8
	clear oil		96	B	$C_{10}H_{10}Cl_2N_2$	C H N Cl	52.4 4.4 12.2 31.0	52.3 4.5 12.0 31.4
	yellow oil		77	B	$C_{10}H_{10}Cl_2N_2$	C H N Cl	52.4 4.4 12.2 31.0	52.2 4.2 11.8 31.4

are readily hydrolyzed in 70% acetic acid to the ethyl 3-(substituted-benzoyl)propionates (**13**). Reaction of intermediates **12** or **13** with hydrazine gave the 6-phenyl-4,5-dihydro-3(2*H*)pyridazinones (**11**) in good yields (12) (see Table IV). Products **11** can also be obtained through nitrile **9** and intermediate γ-keto acids **10**; however, there is no specific advantage to this route except in cases where the α-(aryl)-4-morpholineacetonitriles add poorly to ethyl acrylate but add to acrylonitrile, a better Michael acceptor (see Tables II and III). Hydrolysis of **9** to **10** was accomplished in two steps; (1) hydrolysis with 70% acetic acid to give the ketonitriles; and (2) hydrolysis (6 *N* hydrochloric acid) of the ketonitrile to acid **10**.

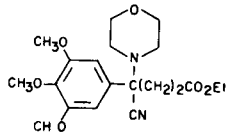
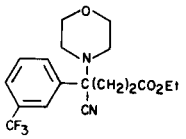
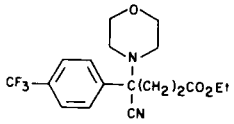
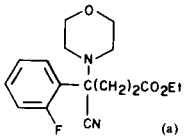
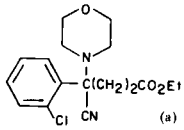
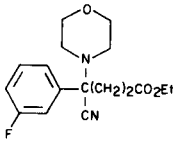
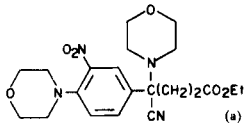
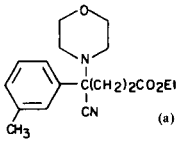
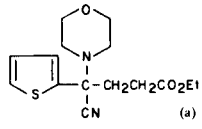
In contrast to the procedure of Stetter, the 4-morpholineacetonitrile derivatives **14** and **15** from *o*-fluoro- and *o*-chlorobenzaldehyde gave good yields of the 1,4-addition products **17** and **18**. *o*-Trifluoromethylbenzaldehyde afforded the 4-morpholineacetonitrile **16**; however, the reaction of ethyl acylate or acrylonitrile with the anion



14, X = Cl
15, X = F
16, X = CF_3

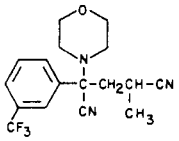
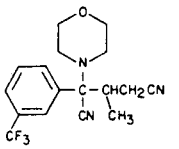
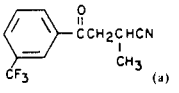
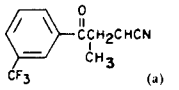
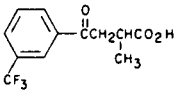
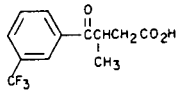
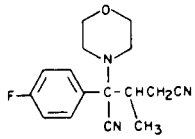
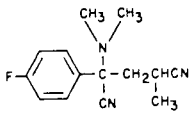
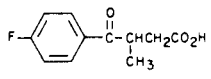
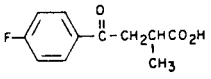
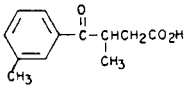
17, X = Cl
18, X = F

Table II

Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula		Analysis Calcd.	Found
	98-100	ethanol	49	C	$C_{20}H_{28}N_2O_6$	C H N	61.2 7.2 7.1	60.8 7.3 7.1
	oil		81	C	$C_{18}H_{21}F_3N_2O_3$	C H N F	58.4 5.7 7.6 15.4	58.3 5.3 7.0 15.2
	96-97	dichloromethane-hexane	57	C	$C_{18}H_{21}F_3N_2O_3$	C H N F	58.4 5.7 7.6 15.4	58.7 5.9 7.6 15.8
	oil		81	D	$C_{17}H_{21}FN_2O_3$			
	oil		98	D	$C_{17}H_{21}ClN_2O_3$			
	88-90	dichloromethane-hexane	44	C	$C_{17}H_{21}FN_2O_3$	C H N F	63.7 6.6 8.8 5.9	63.5 6.8 8.7 6.2
	gum		94	D	$C_{21}H_{28}N_4O_6$			
	oil		99	D	$C_{18}H_{24}N_2O_3$			
	oil(a)		97	D	$C_{15}H_{20}N_2O_3S$			

(a) Used without purification in the subsequent ring closure with hydrazine.

Table III

Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula	Analysis	Calcd.	Found
	88-89	dichloromethane-hexane	64	E	$C_{17}H_{18}F_3N_2O$	C H N F	60.5 5.4 12.5 16.9	61.0 5.5 12.4 17.0
	115-118	chloroform-hexane	55	E	$C_{17}H_{18}F_3N_3O$	C H N F	60.5 5.4 12.5 16.9	60.8 5.4 12.4 17.1
 (a)	yellow oil		89	F	$C_{12}H_{10}F_3NO$			
 (a)	yellow oil		100	F	$C_{12}H_{10}F_3NO$			
	91-93	chloroform-hexane	77	F	$C_{10}H_{11}F_3O_3$	C H F	55.4 4.3 21.9	55.0 4.3 22.1
	oil		50	F	$C_{10}H_{11}F_3O_3$	C H F	55.4 4.5 21.9	55.1 4.5 22.3
	105-107	dichloromethane-hexane	89	E	$C_{16}H_{18}FN_3O$	C H N	66.9 6.3 14.6	66.5 6.3 14.7
	103-105	dichloromethane-hexane	40	E	$C_{14}H_{16}FN_3$	C H N F	68.6 6.6 17.0 7.8	68.7 6.5 17.1 7.7
	71-73		58	F	$C_{11}H_{11}FO_3$	C H F	62.9 5.3 9.0	62.6 5.2 9.0
	122-124		86	F	$C_{11}H_{11}FO_3$	C H F	62.9 5.3 9.0	62.8 5.3 9.1
	60-63		67	F	$C_{12}H_{14}O_3$	C H	69.9 6.8	69.7 6.5

(a) Used in subsequent hydrolysis without purification.

Table IV

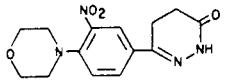
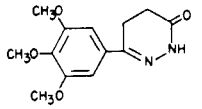
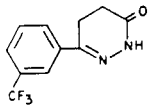
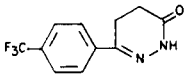
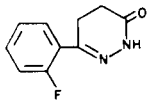
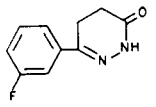
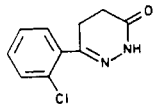
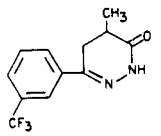
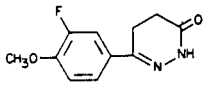
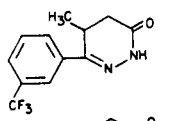
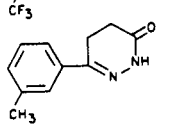
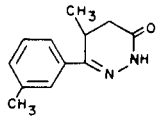
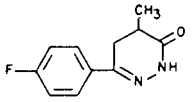
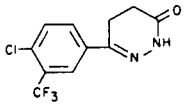
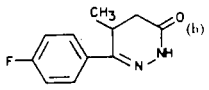
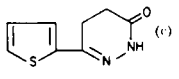
Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula		Analysis Calcd.	Found
	179-181	methanol	78	G	$C_{14}H_{16}N_4O_4$	C H N	55.3 5.3 18.4	55.2 5.5 18.6
	140-141	ethanol	81	G	$C_{13}H_{16}N_2O_4$	C H N	59.1 6.1 10.6	59.1 6.2 10.6
	170-171	chloroform-petroleum ether	67	G	$C_{11}H_9F_3N_2O$	C H N F	54.6 3.8 11.6 23.5	54.3 3.7 11.4 23.1
	177-178	dichloromethane-hexane	65	G	$C_{11}H_9F_3N_2O$	C H N F	54.6 3.8 11.6 23.5	54.6 3.9 11.7 23.4
	119-121	dichloromethane-hexane	56	G	$C_{10}H_9FN_2O$	C H N F	62.5 4.7 14.6 9.9	62.7 4.9 14.8 10.2
	132-134	dichloromethane-hexane	40	G	$C_{10}H_9FN_2O$	C H N F	62.5 4.7 14.6 9.9	62.3 4.8 14.6 10.1
	114-116	chloroform-hexane	63	G	$C_{10}H_9ClN_2O$	C H N Cl	57.6 4.4 13.4 17.0	57.6 4.3 13.4 17.4
	191-193	chloroform-hexane	87	H	$C_{12}H_{11}F_3N_2O$	C H N F	56.3 4.3 10.9 22.3	56.1 4.3 10.8 22.3
	180-183	ethanol	95	H	$C_{11}H_{11}FN_2O_2$	C H N F	59.5 5.0 12.6 8.6	59.4 5.1 12.9 8.3
	142-144	dichloromethane-hexane	87	H	$C_{12}H_{11}F_3N_2O$	C H N F	56.3 4.3 10.9 22.3	56.2 4.6 10.9 22.2
	130-132	dichloromethane-hexane	69	G	$C_{11}H_{12}N_2O$	C H N	70.2 6.4 14.9	69.9 6.3 14.9

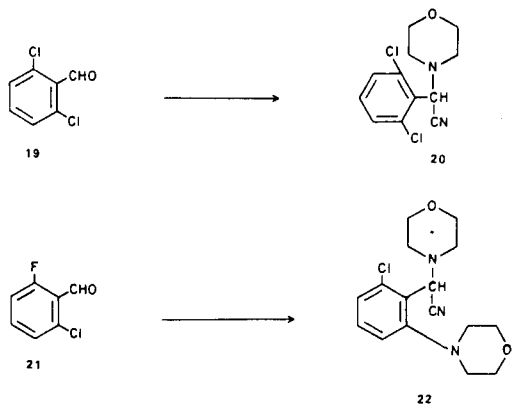
Table IV (continued)

Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula	Analysis	Calcd.	Found
	154-156	dichloromethane-hexane	87	H	$C_{12}H_{14}N_2O$	C H N	71.3 7.0 13.9	71.3 6.9 14.0
	152-154	methanol	79	H	$C_{11}H_{11}FN_2O$	C H N F	64.1 5.4 13.6 9.2	64.0 5.6 13.6 9.0
	195-198	methanol	32 (a)	G	$C_{11}H_8ClF_3N_2O$	C H N Cl F	47.8 2.9 10.1 12.8 20.6	47.4 3.2 10.1 12.7 21.4
 (b)	169-171		80	H	$C_{11}H_{11}FN_2O$	C H N F	64.1 5.4 13.6 9.2	63.7 5.6 13.6 9.5
 (c)	115-117	dichloromethane-hexane	72	G	$C_8H_8N_2SO$			

(a) Yield from α-(4-chloro-3-trifluoromethylphenyl)-4-morpholineacetonitrile and ethyl acrylate followed by reaction with hydrazine without purification of intermediate. (b) Lit. (2) m.p. 170-172°. (c) Lit. (14) m.p. 119-119.5°.

of **16** did not give satisfactory yields of 1,4-addition products.

2,6-Dichlorobenzaldehyde (**19**) gave a good yield of morpholinonitrile (**20**). Steric factors are probably responsible for the failure of **20** to add to ethyl acrylate or acrylonitrile. 2-Fluoro-6-chlorobenzaldehyde (**21**) gave



morpholineacetonitrile (**22**) in which the fluorine was replaced by morpholine.

The 1,4-additions of α-(substituted-phenyl)-4-morpholineacetonitriles to ethyl crotonate and α-methylacrylate proceeded poorly but additions to the better Michael acceptors α-methylacrylonitrile and crotonotrile gave satisfactory yields (see Table III). The use of methylacrylonitrile and crotononitrile allows for the introduction of

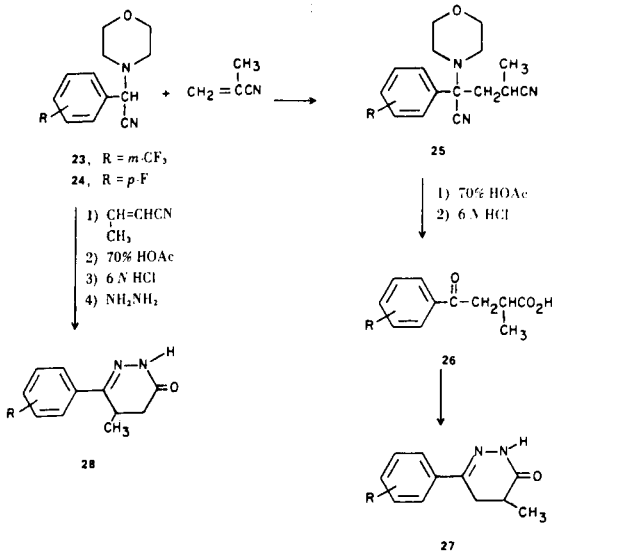


Table V

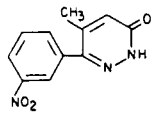
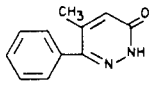
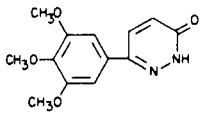
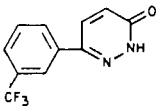
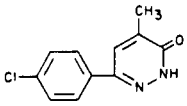
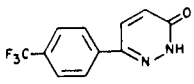
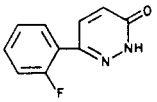
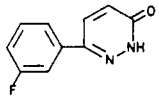
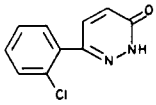
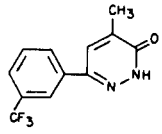
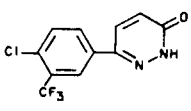
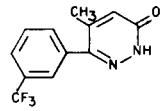
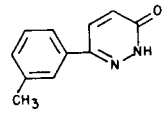
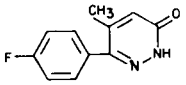
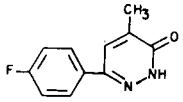
Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula	Analysis	Calcd.	Found
	301-304	DMSO	95	I	$C_{11}H_9N_3O_3$	C H N	57.1 3.9 18.2	56.9 3.9 18.3
	211-213	methanol	93	K	$C_{11}H_{10}N_2O$	C H N	71.0 5.4 15.1	71.0 5.6 15.1
	238-242	DMF-water	90	J	$C_{13}H_{14}N_2O_4$	C H N	59.5 5.4 10.7	59.5 5.4 10.4
	215-218	DMF-water	99	I	$C_{11}H_7F_3N_2O$	C H N F	55.0 2.9 11.7 23.7	55.1 2.9 11.5 23.5
	224-226	ethanol	97	I	$C_{11}H_9ClN_2O$	C H N Cl	59.9 4.1 12.7 16.1	59.9 3.8 12.8 16.5
	191-193	dichloromethane	83	I	$C_{11}H_7F_3N_2O$	C H N F	55.0 2.9 11.7 23.7	55.3 3.1 11.7 24.1
	173-175	dichloromethane-hexane	83	I	$C_{10}H_7FN_2O$	C H N F	63.2 3.7 14.7 10.0	62.9 3.8 14.5 10.3
	207-209	dichloromethane-hexane	99	I	$C_{10}H_7FN_2O$	C H N F	63.2 3.7 14.7 10.0	63.1 3.8 14.8 10.1
	214-216	dichloromethane-hexane	92	I	$C_{10}H_7ClN_2O$	C H N Cl	58.1 3.4 13.6 17.2	57.7 3.4 13.4 17.6
	236-238	methanol	100	I	$C_{12}H_9F_3N_2O$	C H N F	56.7 3.6 11.0 22.4	56.5 3.5 11.1 22.8
	249-251	DMF-water	100	I	$C_{11}H_6ClF_3N_2O$	C H N F Cl	48.1 2.2 10.2 20.8 12.9	48.1 2.3 10.3 21.1 12.8

Table V (continued)

Structure	M.p., °C	Recryst. Solvent	% Yield	Procedure	Formula	Analysis	Calcd.	Found
	226-229		95	I	$C_{12}H_9F_3N_2O$	C H N F	56.7 3.6 11.0 22.4	56.6 3.9 11.1 22.3
	204-206	methanol	50	I (a)	$C_{11}H_{10}N_2O$	C H N	71.0 5.4 15.1	70.9 5.7 15.0
	243-245	methanol	99	I	$C_{11}H_9FN_2O$	C H N F	64.7 4.4 13.7 9.3	64.4 4.5 13.6 9.8
	239-241	dichloromethane	100	I	$C_{11}H_9FN_2O$	C H N F	64.7 4.4 13.7 9.3	64.6 4.6 13.8 9.5

(a) In some reactions a small amount of ring bromination occurred. This was easily moved by hydrogenation in ethanol using 10% Pd/C.

Table VI (a)

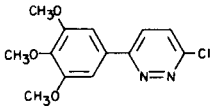
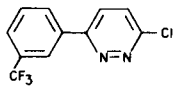
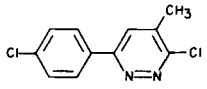
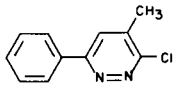
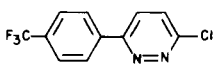
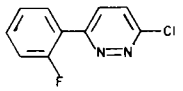
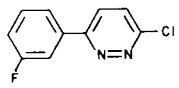
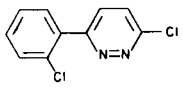
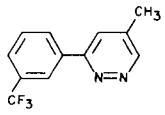
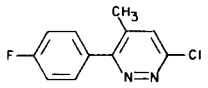
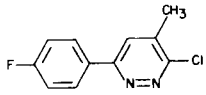
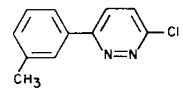
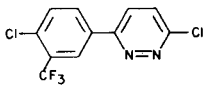
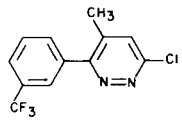
Structure	M.p., °C	Recryst. Solvent	% Yield	Formula	Analysis	Calcd.	Found
	120-121	ethanol	97	$C_{13}H_{13}ClN_2O_3$	C H N Cl	55.6 4.7 10.0 12.6	55.6 4.8 10.2 12.8
	131-133	methanol	100	$C_{11}H_6ClF_3N_2$	C H N Cl F	51.1 2.3 10.8 13.7 22.0	51.0 2.4 10.9 13.5 21.9
	195-197	ethanol	99	$C_{11}H_8Cl_2N_2$	C H N Cl	55.3 3.4 11.7 29.7	55.3 3.4 11.7 29.6
	140-142	ethanol	71	$C_{11}H_9ClN_2$	C H N Cl	64.6 4.4 13.7 17.3	64.3 4.7 13.8 17.3
	186-188	dichloromethane-hexane	87	$C_{11}H_6ClF_3N_2$	C H N Cl F	51.1 2.3 10.8 13.7 22.0	51.2 2.5 10.8 13.7 21.9

Table VI (continued)

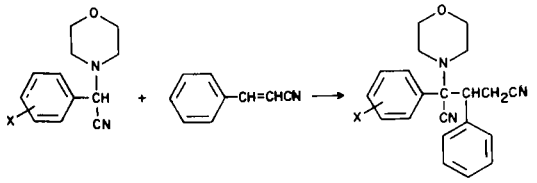
Structure	M.p., °C	Recryst. Solvent	% Yield	Formula	Analysis	Calcd.	Found
	95-96	dichloromethane-hexane	65	$C_{10}H_6ClFN_2$	C H N Cl F	57.6 2.9 13.4 17.0 9.1	57.5 3.0 13.4 17.2 9.2
	133-135	dichloromethane-hexane	91	$C_{10}H_6ClFN_2$	C H N Cl F	57.6 2.9 13.4 17.0 9.1	57.5 3.1 13.4 17.1 9.4
	145-147	chloroform-hexane	95	$C_{10}H_6Cl_2N_2$	C H N Cl	53.4 2.7 12.5 31.5	53.5 2.6 12.2 31.2
	123-126	chloroform-hexane	86	$C_{12}H_8ClF_3N_2$	C H N Cl F	52.9 3.0 10.3 13.0 20.9	52.7 3.0 10.1 13.0 21.1
	153-154	dichloromethane-hexane	95	$C_{11}H_8ClFN_2$	C H N Cl F	59.3 3.6 12.6 15.9 8.5	59.1 3.6 12.6 16.0 8.5
	177-178	dichloromethane-hexane	99	$C_{11}H_8ClFN_2$	C H N Cl F	59.3 3.6 12.6 15.9 8.5	59.3 3.7 12.6 16.0 8.6
	112-113	dichloromethane-hexane	66	$C_{11}H_9ClN_2$	C H N Cl	64.6 4.4 13.7 17.3	64.1 4.3 13.4 17.0
	151-152	dichloromethane-hexane	93	$C_{11}H_5Cl_2F_3N_2$	C H N Cl F	45.1 1.7 9.6 24.2 19.5	44.8 1.8 10.0 23.9 19.3
	120-122	dichloromethane-hexane	93	$C_{12}H_8ClF_3N_2$	C H N Cl F	52.9 3.0 10.3 13.0 20.9	53.3 3.3 10.4 13.1 21.0

(a) All the compounds were prepared according to procedure L in Experimental.

methyl groups in the 4 or 5 positions of 6-phenyl-4,5-dihydro-3(2*H*)pyridazinones as shown in the preparation of **27** and **28**.

The addition of 4-morpholineacetonitriles **23** and **29** to cinnamonitrile gave the phenyl substituted derivatives **30** and **31**. This method allows the introduction of a phenyl or substituted phenyl group in the 5 position of 6-phenyl-3(2*H*)pyridazinones (13).

It should be noted that dehydrogenations of 4,5-dihydro-3(2*H*)pyridazinones with bromine is a general re-



29, X = *p*-Cl
23, X = *m*-CF_3

30, X = *p*-Cl
31, X = *m*-CF_3

action only for those compounds containing 6-phenyl groups without electron donating groups. Bromination of the aromatic ring occurs with 6-(methoxyphenyl) and 6-(thienyl)-4,5-dihydro-3(2*H*)pyridazinones (14). Dehydrogenations of these compounds with the sodium salt of *m*-nitrobenzenesulfonic acid is the only good alternative procedure developed which gave satisfactory yields in the several cases studied (3).

EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus and are uncorrected. Samples for analysis were dried *in vacuo* over Drierite for 18 hours at 50°. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (model 21). Pmr spectra were determined on all compounds reported with a Varian HR-100 spectrometer and chemical shifts (δ) were as expected. Magnesol is a trade name for hydrous magnesium silicate.

Procedure A.

α(α,α,α-Trifluoro-*p*-tolyl)-4-morpholineacetonitrile.

To a solution of 76.0 g. (0.40 mole) of *p*-toluenesulfonic acid in 400 ml. of tetrahydrofuran was added 69.5 g. (0.80 mole) of morpholine. While stirring, 65.0 g. (0.37 mole) of *p*-trifluoromethylbenzaldehyde was added and the mixture was heated on a steam bath for 2 hours. To the cooled reaction mixture was added a slurry of 32.6 g. (0.5 mole) of potassium cyanide in 55 ml. of water. The mixture was refluxed for 18 hours and concentrated under vacuum. The residue was partitioned between chloroform and water. The organic layer was washed with saturated sodium bisulfite and sodium chloride solutions, dried over magnesium sulfate, treated with activated carbon and concentrated to afford 75.0 g. (75%) of tan crystals. A sample was recrystallized from hexane to afford white crystals, m.p. 89-90°.

Anal. Calcd. for $C_{13}H_{13}F_3N_2O$: C, 57.8; H, 4.9; F, 21.1; N, 10.4. Found: C, 57.8; H, 4.8; F, 21.2; N, 10.3.

Procedure B.

α(2,6-Dichlorophenyl)-α(dimethylamino)acetonitrile.

To a slurry of 40.8 g. (0.50 mole) of dimethylamine hydrochloride and 24.5 g. (0.50 mole) of sodium cyanide in 75 ml. of water and 1500 ml. of methanol, was added 75.0 g. (0.40 mole) of 2,6-dichlorobenzaldehyde. The mixture was stirred at room temperature for 18 hours and the solvent was removed. The residue was partitioned between dichloromethane and water. The organic layer was washed with saturated sodium bisulfite and saturated sodium chloride solutions, dried with magnesium sulfate, treated with activated carbon and passed through Magnesol. The filtrate was concentrated to afford 95.0 g. (96%) of a yellow oil. A sample was passed through Magnesol again to afford a yellow oil.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2$: C, 52.4; H, 4.4; Cl, 31.0; N, 12.2. Found: C, 52.3; H, 4.5; Cl, 31.4; N, 12.0.

Procedure C.

Ethyl γ-Cyano-γ-(3,4,5-trimethoxyphenyl)-4-morpholinebutyrate.

To a solution of 12.5 g. (42.8 mmoles) of α(3,4,5-trimethoxyphenyl)-4-morpholineacetonitrile in 125 ml. of tetrahydrofuran was added 60 drops of 30% potassium hydroxide in ethanol. A solution of 6.25 ml. of ethyl acrylate (63.0 mmoles) in 50 ml. of tetrahydrofuran was added dropwise over 10 minutes and the mixture was stirred at room temperature for 1.5 hours. A slight exotherm was noted during the addition. The solvent was removed and the concentrate stripped with toluene. Trituration of the residue with ether afforded 8.25 g. (49%) of white crystals, m.p. 105-107°. A sample was recrystallized from ethanol to afford white crystals, m.p. 108-109°.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.2; H, 7.2; N, 7.1. Found: C, 60.8; H, 7.3; N, 7.1.

Procedure D.

Ethyl γ-Cyano-γ-(*m*-trifluoromethylphenyl)-4-morpholinebutyrate.

To a stirred solution of 5.0 g. (18.5 mmoles) of α(*m*-trifluoromethylphenyl)-4-morpholineacetonitrile in 200 ml. of tetrahydrofuran was added 30 drops of 30% potassium hydroxide in ethanol followed after 10 minutes by the rapid addition of 10 ml. (0.1 mole) of ethyl acrylate. After stirring 1 hour, the same quantities of base and ethyl acrylate were added again. Stirring was continued for two hours and the solvent removed under vacuum. Toluene was added several times and the solvent removed under vacuum. The residue was stirred with ether, filtered and the solvent removed to give 5.56 g. (81%) of a yellow oil. The product was columned on silica gel using chloroform to afford a yellow oil.

Anal. Calcd. for $C_{18}H_{21}F_3N_2O_3$: C, 58.4; H, 5.7; F, 15.4; N, 7.6. Found: C, 58.3; H, 5.3; F, 15.2; N, 7.0.

Procedure E.

4-Methyl-2-morpholino-2-(*m*-trifluoromethylphenyl)glutaronitrile.

To a solution of 60.0 g. (0.22 mole) of α(*m*-trifluoromethylphenyl)-4-morpholineacetonitrile in 20 ml. of tetrahydrofuran was added 5 ml. of a solution of 30% potassium hydroxide in methanol followed by 22.0 ml. (0.26 mole) of methylacrylonitrile. The mixture was stirred at room temperature for 18 hours. The solvent was removed and the concentrate stripped several times with toluene. The residue was dissolved in chloroform and passed through Magnesol. The filtrate was concentrated to a yellow oil which was stirred with ether-hexane to afford 47.0 g. (64%) of cream colored crystals, m.p. 88-90°. A sample was recrystallized from dichloromethane-hexane to afford white crystals, m.p. 88-90°.

Anal. Calcd. for $C_{17}H_{18}F_3N_3O$: C, 60.5; H, 5.4; F. 16.9; N, 12.5. Found: C, 61.0; H, 5.5; F, 17.0; N, 12.4.

Procedure F.

2-Methyl-3-(*m*-trifluoromethylbenzoyl)propionic Acid.

A mixture of 11.3 g. (33.5 mmoles) of 4-methyl-2-morpholino-2-(*m*-trifluoromethylphenyl)glutaronitrile, 75 ml. of acetic acid and 5 ml. of water was heated on a steam bath for 18 hours. The solvent was removed and the residue dissolved in dichloromethane and passed through Magnesol. The filtrate was concentrated to afford 7.2 g. of dark yellow oil which was added to 150 ml. of 6 *N* hydrochloric acid. The mixture was refluxed 24 hours, cooled and extracted with chloroform. The organic layer was passed through Magnesol and the solvent removed. The residue was

m.p. 72-75°. A sample was recrystallized from chloroform-hexane to yield tan crystals, m.p. 91-93°.

Anal. Calcd. for $C_{12}H_{11}F_3O_3$: C, 55.4; H, 4.3; F, 21.9. Found: C, 55.0; H, 4.3; F, 22.1.

Procedure G.

4,5-Dihydro-6-(3,4,5-trimethoxyphenyl)-3(2*H*)pyridazinone.

A solution of 4.65 g. (11.9 mmoles) of ethyl γ-cyano-γ-(3,4,5-trimethoxyphenyl)-4-morpholinebutyrate and 0.65 ml. (13.0 mmoles) of hydrazine hydrate in 50 ml. of ethanol was refluxed for 24 hours. The mixture was chilled in an ice bath and filtered to give 2.52 g. (81%) of white crystals, m.p. 140-141°. A sample was recrystallized from ethanol to afford white crystals, m.p. 140-141°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.1; H, 6.1; N, 10.6. Found: C, 59.1; H, 6.2; N, 10.6.

Procedure H.

6-(3-Fluoro-4-methoxyphenyl)-4,5-dihydro-3(2*H*)pyridazinone.

A solution of 49.9 g. (0.2 mole) of 3-(3-fluoro-4-methoxybenzoyl)propionic acid, 15.0 g. (0.3 mole) of hydrazine hydrate was refluxed for 18 hours. Cooling in ice and filtering afforded 46.5 g. (95%) of yellow crystals, m.p. 175-179°. A sample was recrystallized from ethanol several times (following activated carbon treatment) to afford white crystals, m.p. 180-183°.

Anal. Calcd. for $C_{11}H_{11}FN_2O_2$: C, 59.5; H, 5.0; F, 8.6; N, 12.6. Found: C, 59.4; H, 5.1; F, 8.3; N, 12.9.

Procedure I.

6-(*m*-Trifluoromethylphenyl)-3(2*H*)pyridazinone.

To a solution of 14.55 g. (60.0 mmoles) of 4,5-dihydro-6-(*m*-trifluoromethylphenyl)-3(2*H*)-pyridazinone in 225 ml. of acetic acid was added 10% of a solution of 3.3 ml. (65.0 mmoles) of bromine in 25 ml. of acetic acid. While warming on a steam bath the remainder of the bromine solution was added slowly over a 10 minute period. Following an additional 30 minutes of heating, the reaction was concentrated free of solvent and the concentrate washed with water, filtered and air dried to give 14.3 g. (99%) of cream colored crystals, m.p. 212-215°. A sample was recrystallized from *N,N*-dimethylformamide-water, after Darco treatment, to yield white crystals, m.p. 215-218°.

Anal. Calcd. for $C_{11}H_7F_3N_2O$: C, 55.0; H, 2.9; F, 23.7; N, 11.7. Found: C, 55.1; H, 2.9; F, 23.5; N, 11.5.

Procedure J.

6-(3,4,5-Trimethoxyphenyl)-3(2*H*)pyridazinone.

A solution of 7.8 g. (29.5 mmoles) of 4,5-dihydro-6-(3,4,5-trimethoxyphenyl)-3(2*H*)pyridazinone, 8.4 g. (37.0 mmoles) of *m*-nitrobenzenesulfonic acid sodium salt and 5.9 g. (0.15 mole) of sodium hydroxide in 100 ml. of water was heated on a steam bath for 2 hours. The reaction mixture was treated with Darco, filtered and the filtrate cooled in an ice bath. The mixture was acidified with concentrated hydrochloric acid, filtered and the solid washed with water to afford 6.95 g. (90%) of yellow crystals, m.p. 223-228°. A sample was recrystallized from DMF-water to afford cream colored crystals, m.p. 238-242°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.4; N, 10.7. Found: C, 59.5; H, 5.4; N, 10.4.

Procedure K.

5-Methyl-6-phenyl-3(2*H*)pyridazinone.

A slurry of 10.0 g. (37.8 mmoles) of 6-(*p*-bromophenyl)-5-methyl-3(2*H*)pyridazinone and 1.0 g. of 10% Pd/C in 150 ml. of ethyl alcohol and 50 ml. of ammonium hydroxide was shaken in a Parr apparatus under 40 lb of hydrogen pressure for 4 hours. An external heating jacket kept the Parr bottle at 50°. Following filtration and concentration of the filtrate the resulting white solid was washed well with water to afford 6.5 g. (93%) of white crystals, m.p. 214-216°. Recrystallization from methanol afforded 5.5 g. of white crystals, m.p. 211-213°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 71.0; H, 5.4; N, 15.1. Found: C, 71.0; H, 5.6; N, 15.1.

Procedure L.

3-Chloro-6-(3,4,5-trimethoxyphenyl)pyridazine.

A solution of 31.19 g. (0.11 mole) of 6-(3,4,5-trimethoxyphenyl)-3(2*H*)pyridazinone in 300 ml. of phosphorus oxychloride was heated on a steam bath for 18 hours. The solvent was removed to afford a dark oil which was stirred with crushed ice. The mixture was filtered and the solid washed with water to give 30.0 g. (97%) of gray crystals, m.p. 110-114°. A sample was recrystallized from ethanol to afford white crystals, m.p. 120-121°.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.6; H, 4.7; Cl, 12.6; N, 10.0. Found: C, 55.6; H, 4.8; Cl, 12.8; N, 10.2.

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