HETEROCYCLES FROM NITRILE IMINES. PART IV.[1] CHIRAL 4,5-DIHYDRO-1,2,4-TRIAZIN-6-ONES

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Abstract ——→ The reaction of nitrile imines (II) with α-amino esters (III) proceeds with no detectable racemization and constitutes a convenient synthetic route to 4,5-dihydro-1,2,4-triazin-6-ones (IV). Permanganate oxidation of the heterocycles (IV) affords the corresponding 1,2,4-triazin-6-ones (V). The reaction of (II) with β-amino esters gives the respective acyclic amidrazone adducts (VI).

Addition reactions of a variety of nucleophilic species onto nitrile imines (II) provide access to several acyclic chemical systems.[2-4] Of particular interest is the reaction of (II) with nucleophilic substrates incorporating suitably located electrophilic centers leading, via cyclization of the intermediate adducts, to various heterocyclic products.[4-9] The reaction of (II) with α-amino esters remains, however, unexplored in the literature.

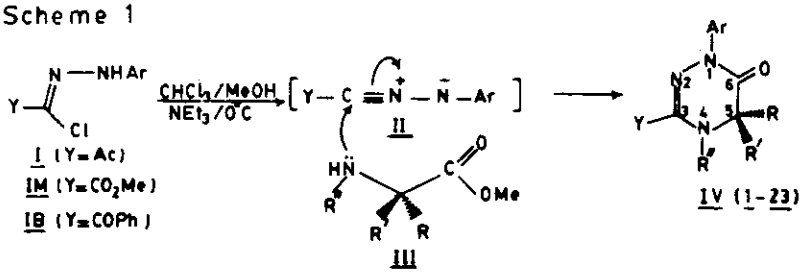
Recently, we found that nitrile oxides reacted with α-amino esters (III) to afford 4,5-dihydro-1,2,4-oxadiazin-6-ones.[10] As a consequence, their aza-analogues, 4,5-dihydro-1,2,4-triazin-6-ones, are expected to be formed from the reaction of (II) and (III).

In the present work, we find that α-amino esters (III) react readily with nitrile imines (II), generated in situ from the action of NEt_3 onto the hydrazonoyl chlorides (I), yielding the corresponding 4,5-dihydro-1,2,4-triazin-6-ones (IV; 1-23) (Scheme 1).

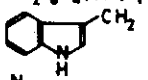
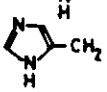
The hydrazonoyl chlorides (IM; Y=CO_2Me) have been previously described.[8]

The related hydrazonoyl chlorides (Ia-k; Y=Ac) (Table 1 and Scheme 1) were prepared via the direct coupling of arenediazonium chlorides with 3-chloropentane-2,4-dione (Japp-Klingemann reaction).[11] The hydrazonoyl chloride (IaB; Y=COPh, X=H) was prepared by the reaction of benzenediazonium chloride with phenacyl chloride as previously reported.[12]

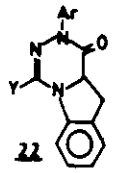
Scheme 1



Compounds IV(1-23):

No	R	No	R	No	R′, R	No	R′, R
1	H	9	$CH_2CH_2CO_2Me$	15	Me Me	18	Me H
2	Me	10	Ph	16	$-(CH_2)_4-$	19	$PhCH_2$ H
3	$CHMe_2$	11	$PhCH_2$	17	$-(CH_2)_5-$	20	$-(CH_2)_5-$
4	CH_2CHMe_2	12	$CH_2C_6H_4(OH)$-p			21	$-(CH_2)_4-$
5	CH(Me)Et	13					
6	CH_2CH_2SMe			15–17 : R″=H		18–21 : R′=H	
7	CH_2OH	14					
8	CH_2CO_2Me						

1–14 : R′=R″=H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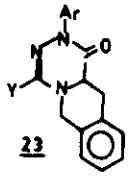
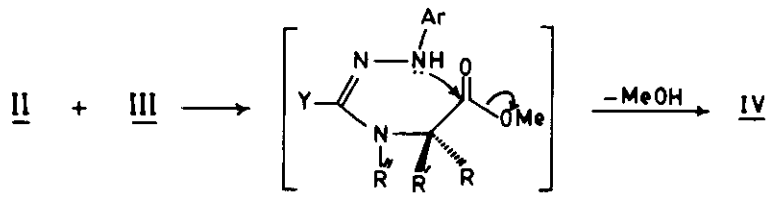

23

(Ar = )

Entry	a	b	c	d	e	f	g	h	i	j	k
X	H	Me	OMe	F	Cl	Br	I	CN	Ac	NO_2	CO_2Me

Primary and secondary amines add readily onto nitrile imines (II) to yield the respective amidrazone adducts.[2-4] Likewise, and by analogy to their reactions with nitrile oxides,[10] α-amino esters (III) are expected to add onto nitrile imines and give initially the corresponding (Z)-amidrazone esters (IVA), shown below, as the kinetically controlled products. The latter transient acyclic adducts undergo cyclization, to yield the respctive heterocycles (IV).



(Z)-(IVA)

Table 1. Physical and Analytical Data for the Hydrazonoyl Chlorides (I)[a].

		Calcd (%)			Found (%)		
Compd	mp (°C)	C	H	N	C	H	N
Ig	170-171[b]	33.52	2.50	8.69	33.38	2.44	8.62
Ih	229-230[c]	54.19	3.64	18.96	53.92	3.55	18.80
Ii	194-195[c]	55.36	4.65	11.74	55.18	4.62	11.60
Ik	203-204[c]	51.88	4.35	11.00	51.62	4.28	10.86

[a]The following hydrazonoyl chlorides, employed in this work, were previously characterized; their melting points (°C) as provided below, are in accordance with the literature values (not given here): Ia,[9,13,14] mp 141-142; Ib,[9] mp 150-151; Ic,[9,15] mp 119-120; Id,[16] mp 148-149; Ie,[9,14] mp 178-179; If,[3,5] mp 166-167; Ij,[9] mp 234-235; IaB,[12] mp 135-136. Alternative syntheses of the following pyruvoyl chloride phenylhydrazones have been described: 1a;[17-19] 1b;[18] 1e.[19] [b]Recrystallized from chloroform/pet. ether (bp 40-60°C); this compound was cited in the literature.[20] [c]Recrystallized from THF/pet. ether.

The assignment of the dihydro-1,2,4-triazin-6-one structure (IV) to these heterocyclic products (1-23) is based on elemental analysis (Table 2) and spectral data (Table 3).

It is worth noting that glycine and α-alanine esters have reacted, in a previous work,[10] with nitrile oxides to give the correspondig acyclic amidoxime adducts. This behaviour is in contrast with that observed here

Table 2. Physical and Analytical Data for Compounds (IV; 1-23).

Compd	Y	mp (°C)	Yield[a] (%)	$[\alpha]_D^{20}$	Mol. Formula	[M]†	Calcd/Found (%) C	H	N
1e	Ac	204-205	70		$C_{11}H_{10}N_3O_2Cl$	251/253	52.50 52.71	4.00 4.08	16.70 16.76
1g	Ac	188-189	66		$C_{11}H_{10}N_3O_2I$	343	38.51 38.77	2.94 3.19	12.25 12.25
1i	Ac	182-183	72		$C_{13}H_{13}N_3O_3$	259	60.23 60.23	5.05 5.14	16.21 16.11
2c	Ac	108-109	32	+22.2°	$C_{13}H_{15}N_3O_3$	261	59.76 59.81	5.79 5.82	16.08 16.05
2d	Ac	141-142	60	+33.4°	$C_{12}H_{12}N_3O_2F$	249	57.83 58.18	4.85 4.83	16.86 17.15
2e	Ac	142-143	65	+30.7°	$C_{12}H_{12}N_3O_2Cl$	265/267	54.25 54.44	4.55 4.73	15.81 15.91
2f	Ac	155-156	72	+24.7°	$C_{12}H_{12}N_3O_2Br$	309/311	46.47 46.49	3.90 3.84	13.55 13.65
3d	Ac	112-113	65	-202.6°	$C_{14}H_{16}N_3O_2F$	277	60.64 60.75	5.82 6.00	15.15 15.13
3e	Ac	141-142	62	-215.0°	$C_{14}H_{16}N_3O_2Cl$	293/295	57.24 57.35	5.49 5.64	14.30 14.50
3jM	CO_2Me	131-132	50	-219.8°	$C_{14}H_{16}N_4O_5$	320	52.50 52.51	5.03 5.10	17.49 17.36
4d	Ac	90-91	74	-170.4°	$C_{15}H_{18}N_3O_2F$	291	61.84 61.98	6.23 6.22	14.42 14.67
4e	Ac	131-132	65	-181.4°	$C_{15}H_{18}N_3O_2Cl$	307/309	58.54 58.65	5.89 5.87	13.65 13.78
4f	Ac	123-124	62	-163.6°	$C_{15}H_{18}N_3O_2Br$	351/353	51.15 51.13	5.51 5.18	11.93 11.70
4h	Ac	156-157	74	-211.1°	$C_{16}H_{18}N_4O_2$	298	64.41 64.61	6.08 6.11	18.78 19.04
5d	Ac	88-89	65	-191.7°	$C_{15}H_{18}N_3O_2F$	291	61.84 61.97	6.23 6.21	14.42 14.43
5e	Ac	129-130	50	-204.3°	$C_{15}H_{18}N_3O_2Cl$	307/309	58.54 58.77	5.89 5.89	13.65 13.82
5f	Ac	124-125	45	-180.8°	$C_{15}H_{18}N_3O_2Br$	351/353	51.15 51.19	5.15 5.18	11.93 11.87
5h	Ac	135-136	55	-240.0°	$C_{16}H_{18}N_4O_2$	298	64.41 64.46	6.08 5.96	18.78 18.79
6d	Ac	86-87	70	-79.7°	$C_{14}H_{16}N_3O_2SF$	309	54.36 54.21	5.21 5.19	13.58 13.74

Cont. Table 2

6e	Ac	75-76	60	-87.1°	$C_{14}H_{16}N_3O_2SCl$	325/ 327	51.61 51.74	4.95 5.06	12.90 13.11
7d	Ac	141-142	45	+55.6°	$C_{12}H_{12}N_3O_3F$	265	54.34 54.44	4.56 4.46	15.84 15.92
7e	Ac	163-164	62	+57.1°	$C_{12}H_{12}N_3O_3Cl$	281/ 283	51.17 51.34	4.29 4.43	14.92 14.95
8d	Ac	161-162	72	-87.2°	$C_{14}H_{14}N_3O_4F$	307	54.72 54.58	4.59 4.67	13.68 13.40
8e	Ac	146-147	75	-87.4°	$C_{14}H_{14}N_3O_4Cl$	323/ 325	51.94 51.83	4.36 4.53	12.98 12.88
9d	Ac	109-110	92	-77.4°	$C_{15}H_{16}N_3O_4F$	321	56.07 56.10	5.02 5.15	13.08 13.27
9e	Ac	133-134	80	-84.8°	$C_{15}H_{16}N_3O_4Cl$	337/ 339	53.34 53.24	4.77 4.83	12.44 12.46
(D)-10a	Ac	174-175	65	+154.2°	$C_{17}H_{15}N_3O_2$	293	69.61 69.43	5.15 5.07	14.32 14.18
(±)-10a	Ac	150-151	68		$C_{17}H_{15}N_3O_2$	293	69.61 69.52	5.15 5.10	14.32 14.24
(D)-10jM	CO_2Me	154-155	62	+227.6°	$C_{17}H_{14}N_4O_5$	354	57.63 57.66	3.98 4.03	15.81 15.88
11aB	COPh	145-146	80	-222.4°	$C_{23}H_{19}N_3O_2$	369	74.78 74.67	5.18 5.29	11.37 11.36
11dM	CO_2Me	81-82	70	-172.1°	$C_{18}H_{16}N_3O_3F$	341	63.34 63.11	4.72 5.00	12.31 12.04
11e	Ac	132-133	75	-250.6°	$C_{18}H_{16}N_3O_2Cl$	341/ 343	63.25 63.46	4.72 4.79	12.29 12.44
12b	Ac	173-174	45	-252.6°	$C_{19}H_{19}N_3O_3$	337	67.64 67.68	5.68 5.87	12.45 12.45
12e	Ac	177-178	55	-250.0°	$C_{18}H_{16}N_3O_3Cl$	357/ 359	60.43 60.18	4.51 4.70	11.74 11.72
12f	Ac	179-180	65	-243.4°	$C_{18}H_{16}N_3O_3Br$	401/ 403	53.75 53.66	4.01 3.90	10.45 10.37
13d	Ac	157-158	72	-102.3°	$C_{20}H_{17}N_4O_2F$	364	65.93 66.08	4.70 4.88	15.38 15.38
13e	Ac	172-173	65	-123.7°	$C_{20}H_{17}N_4O_2Cl$	380/ 382	63.08 63.33	4.50 4.59	14.71 14.73
14e	Ac	205-206	30	-41.7°	$C_{15}H_{14}N_5O_2Cl$	331/ 333	54.31 54.53	4.25 4.16	21.11 20.84
15a	Ac	136-137	82		$C_{13}H_{15}N_3O_2$	245	63.66 63.71	6.16 6.39	17.13 17.36

Cont. Table 2

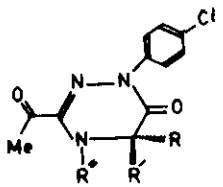
15d	Ac	128-129	75		$C_{13}H_{14}N_3O_2F$	263	59.31 5.36 15.96 59.18 5.28 15.94
15e	Ac	143-144	72		$C_{13}H_{14}N_3O_2Cl$	279/ 281	55.82 5.04 15.02 55.63 5.06 15.19
16a	Ac	102-103	60		$C_{15}H_{17}N_3O_2$	271	66.40 6.32 15.49 66.18 6.45 15.59
16b	Ac	125-126	62		$C_{16}H_{19}N_3O_2$	285	67.35 6.71 14.73 67.08 6.87 14.99
16bM	CO_2Me	144-145	55		$C_{16}H_{19}N_3O_3$	301	63.77 6.35 13.94 63.81 6.41 13.71
16d	Ac	104-105	72		$C_{15}H_{16}N_3O_2F$	289	62.27 5.57 14.52 62.09 5.54 14.49
16dM	CO_2Me	164-165	60		$C_{15}H_{16}N_3O_3F$	305	59.01 5.28 13.76 58.80 5.24 13.85
16e	Ac	128-129	78		$C_{15}H_{16}N_3O_2Cl$	305/ 307	58.92 5.27 13.74 59.02 5.32 13.77
16k	Ac	128-129	50		$C_{17}H_{19}N_3O_4$	329	62.00 5.81 12.76 62.04 6.01 12.89
17a	Ac	103-104	45		$C_{16}H_{19}N_3O_2$	285	67.35 6.71 14.73 67.05 6.92 14.49
17b	Ac	108-109	75		$C_{17}H_{21}N_3O_2$	299	68.21 7.07 14.04 67.85 7.31 13.96
17d	Ac	83-84	60		$C_{16}H_{18}N_3O_2F$	303	63.35 5.98 1385 63.04 5.84 13.75
17e	Ac	145-146	70		$C_{16}H_{18}N_3O_2Cl$	319/ 321	60.09 5.67 13.14 59.89 5.53 13.46
17k	Ac	122-123	65		$C_{18}H_{21}N_3O_4$	343	62.96 6.16 12.24 62.57 6.27 12.09
18d	Ac	86-87	72		$C_{12}H_{12}N_3O_2F$	249	57.83 4.85 16.86 57.66 4.86 16.68
18e	Ac	80-81	70		$C_{12}H_{12}N_3O_2Cl$	265/ 267	54.25 4.55 15.81 54.17 4.56 15.44
19d	Ac	97-98	78		$C_{18}H_{16}N_3O_2F$	325	66.45 4.96 12.92 66.22 5.05 12.82
19e	Ac	71-72	55		$C_{18}H_{16}N_3O_2Cl$	341/ 343	63.25 4.72 12.29 63.31 4.75 12.49
20e	Ac	102-103	65	$+547.5^{\circ}$	$C_{14}H_{14}N_3O_2Cl$	291/ 293	57.64 4.84 14.40 57.81 4.87 14.32
20k	Ac	116-117	62	$+546.6^{\circ}$	$C_{16}H_{17}N_3O_4$	315	60.94 5.43 13.33 60.75 5.52 13.49

cont. Table 2.

(±)-21b	Ac	73-74	55	$C_{16}H_{19}N_3O_2$	285	67.35 6.71 14.73 67.26 6.73 14.65
(±)-21d	Ac	72-73	68	$C_{15}H_{16}N_3O_2F$	289	62.27 5.57 14.52 62.03 5.51 14.37
(±)-21e	Ac	62-63	60	$C_{15}H_{16}N_3O_2Cl$	305/ 307	58.92 5.27 13.74 58.99 5.36 13.64
(±)22a	Ac	199-200	50	$C_{18}H_{15}N_3O_2$	305	70.81 4.95 13.76 70.94 5.03 13.98
(±)-22d	Ac	174-175	82	$C_{18}H_{14}N_3O_2F$	323	66.87 4.36 13.00 66.65 4.22 12.85
(±)-22e	Ac	131-132	70	$C_{18}H_{14}N_3O_2Cl$	339/ 341	63.63 4.15 12.37 63.56 4.14 12.42
(±)-23a	Ac	112-113	55	$C_{19}H_{17}N_3O_2$	319	71.46 5.37 13.16 71.66 5.45 13.37
(±)-23d	Ac	155-156	84	$C_{19}H_{16}N_3O_2F$	337	67.65 4.78 12.46 67.60 4.78 12.48
(±)-23dM	CO_2Me	166-167	65	$C_{19}H_{16}N_3O_3F$	353	64.58 4.56 11.89 64.56 4.43 12.04
(±)-23e	Ac	151-152	72	$C_{19}H_{16}N_3O_2Cl$	353/ 355	64.50 4.56 11.88 64.56 4.63 12.00

[a]Based on recrystallized, analytically pure product.

Table 3. The Chemical Shifts, δ (ppm), for the Different Protons[a] of Model Compounds (IV).



IV	COMe (3H,s)	R	R'	R''
1e	2.47	H 4.16(2H,d); J=2 Hz	H	H 5.86(1H,br s)
2e	2.47	Me 1.5(3H,d); J=8 Hz	H 4.28(1H,dq) J=2,7 Hz	H 5.86(1H,br s)
3e	2.47	CH 2.40(1H,m) $(Me)_2$ 1.04(3H,d); J=7 Hz 0.96(3H,d); J=7 Hz	H 4.05(1H,dd) J=2,6 Hz	H 5.90(1H,br s)

Cont. Table 3

4e	2.47	CH_2 | CH | $(Me)_2$	1.74(2H,m) 1.66(1H,m) 1.01(3H,d); J=7 Hz 0.96(3H,d); J=7 Hz	H 4.16(1H,dt) J=2,6 Hz	H 5.88(1H,br s)
5e	2.47	CHMe | CH_2Me	2.03(1H,m) 1.02(3H,d); J=7 Hz 1.35(2H,m) 0.96(3H,t); J=7 Hz	H 4.12(1H,dd) J=2,6 Hz	H 5.88(1H,br s)
6e	2.47	CH_2 | CH_2 | SMe	2.20(2H,m) 2.66(2H,m) 2.11(3H,s)	H 4.33(1H,dt) J=2,7 Hz	H 6.11(1H,br s)
7e	2.48	CH_2 | | OH	3.93(1H,d) J=7 Hz 4.00(1H,d); J=7 Hz	H 4.30(1H,dt) J=2,6 Hz	H 6.07(1H,br s)
8e	2.46	CH_2 | CO_2Me	2.96(2H,m) 3.74(3H,s)	H 4.56(1H,ddd) J=2,4,10 Hz	H 6.38(1H,br s)
9e	2.47	CH_2 | CH_2 | CO_2Me	2.52(2H,m) 2.24(2H,t); J=7 Hz 3.68(3H,s)	H 4.26(1H,dt) J=2,7 Hz	H 6.10(1H,br s)
11e	2.34	CH_2 | C_6H_5	3.05(2H,m) 7.05-7.35(5H,m)	H 4.42(1H,dt) J=2,7 Hz	H 5.82(1H,br s)
15e	2.48	Me	1.48(6H,s)	Me	H 5.72(1H,br s)
16e	2.47		$-CH_2-(CH_2)_2-CH_2-$ 1.57-1.92(8H,m)		H 5.83(1H,br s)
17e	2.48		$-CH_2-(CH_2)_3-CH_2-$ 1.28-2.02(10H,m)		H 6.10(1H,br s)
18e	2.46	H	3.96(2H,s)	H	Me 3.14(3H,s)
19e	2.51	H	3.88(2H,s)	H	CH_2 4.72(2H,s) | C_6H_5 7.33(5H,s)

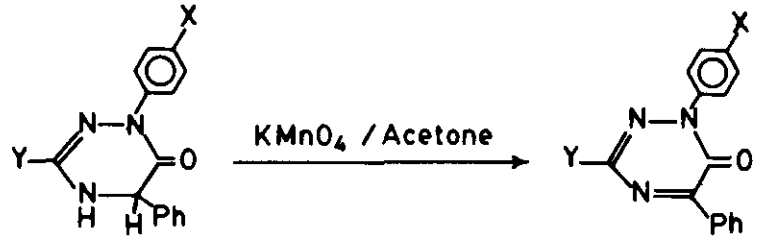
[a]The aromatic protons of the aryl ring at N-1 appear as two doublets (AB-system, J=8 Hz) in the range δ 7.25-7.64 ppm (4H).

for their reaction with nitrile imines giving the cyclized products (IV;1 and 2).

The reaction conditions, employed in the production of compounds (IV), are quite mild such that the center of chirality is presumed to be unaffected, and hence the chiral heterocycles (IV) are expected to be optically pure. This was confirmed by optical purity determination for compound (10a), as a model of this series, by ^{1}H-nmr spectral measurements using tris 3-[heptafluoropropylhydroxymethylene-(d)-camphorato]europium (III), $Eu(hfc)_3$, as the chiral lanthanide shift reagent (LSR method).[22] The criterion for optical purity was the signal for C_3-acetyl methyl protons at 2.53 ppm. This singlet of (±)-10a was resolved into two diastereotopic singlets at 2.66 and 2.70 ppm, of equal integrated peak areas, after the addition of $Eu(hfc)_3$ (molar ratio of [LSR] / [substrate] $\leq$ 0.075). No such splitting was observed for the case of D-(+)-10a in the presence of $Eu(hfc)_3$ up to 0.25 molar ratio (δ =2.95 ppm). A parallel trend was also observed for the C_5-methine proton's signal (δ =5.26 ppm (1H, d), J_{CH-NH}=1.5 Hz). These results indicate that D-10a, and by inference all the chiral compounds (IV;2-14 and 20), is optically pure. Hence the reaction between I and III, leading to IV, proceeds with no detectable racemization.

Permanganate oxidation of (IV), performed on model compounds (10a and jM) gave the respective 1,2,4-triazin-6-ones (V; 24a and jM) (Scheme 2, Table 4).

Scheme 2



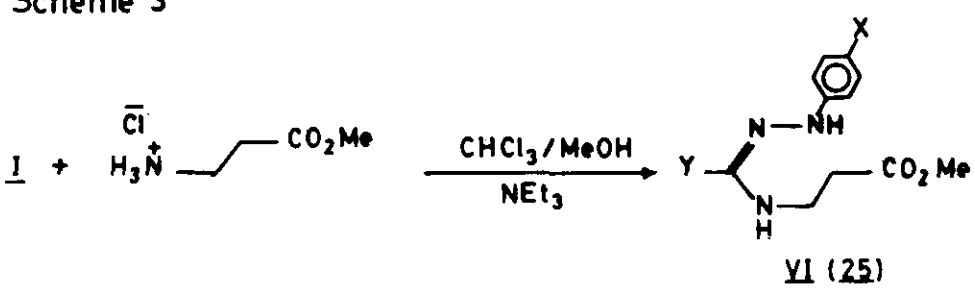
IV(10) V(24)

Table 4. Physical and Analytical Data for Compounds (V;24) and (VI;25).

Compd	Y	X	mp(°C)	Yield (%)	Mol.Formula	[M]$^+$	Calcd/Found (%) C	H	N
24a	Ac	H	112-113	62	$C_{17}H_{13}N_3O_2$	291	70.09 69.87	4.50 4.70	14.42 14.38
24jM	CO_2Me	NO_2	214-215	70	$C_{17}H_{12}N_4O_5$	352	57.96 58.07	3.43 3.59	15.90 16.08
25d	Ac	F	89-90	75	$C_{13}H_{16}N_3O_3F$	281	55.51 55.35	5.73 5.78	14.94 14.87
25e	Ac	Cl	91-92	60	$C_{13}H_{16}N_3O_3Cl$	297/ 299	52.44 52.47	5.42 5.76	14.11 14.07

The reaction of β-alanine methyl ester with hydrazonoyl chlorides (I) yielded, however, the corresponding acyclic amidrazone adducts (VI;25d and e) (Scheme 3).

Scheme 3



VI (25)

Structural Assignment of (V) and (VI) is supported by elemental analysis (Table 4), and spectral data.

Literature routes, applicable to the synthesis of 5-substituted 4,5-dihydro-1,2,4-triazin-6-ones, have so far been confined to the reaction of hydrazine with ethyl α-(N-thioacyl)aminocarboxylate,[22] or with methyl α-(dimethylaminomethyleneamino)carboxylate.[23] The versatile and efficient one-pot synthesis, described in the present work, utilizes readily available inexpensive reactants (α-chlorohyrazones and α-amino esters) and gives good yields of the respective dihydro-1,2,4-triazin-6-ones in

analytically pure crystalline forms. The reaction is conveniently conducted at or below room temperature, and provides direct access to a variety of substituents at N-1, C-3, and C-5 heteroring positions. Evidently, this new viable route avoids racemization, and is of wide scope and generality so that it competes favourably with the methods reported[22,23] for the preparation of related dihydro-1,2,4-triazin-6-ones in which only a limited number of chiral analogues were described.

It is worth mentioning that the 1,2,4-triazine entity, fused to pyrimidin-2,4-dione, is found in the N-methylated pyrimido[4,5,e]-1,2,4-triazine-5,7-diones, a class of naturally occurring antibiotics[24] (e.g. reumycin[25] and toxoflavin[26]). A number of synthetic 1,2,4-triazin-3-ones (e.g. metribuzin) and -5-ones were also reported to possess pronounced herbicidal activity,[27,28] while certain others showed blood platelet aggregation-inhibition activity.[29] Interest in the bioassay of the isomeric 1,2,4-triazin-6-ones might be stimulated by their facile synthesis disclosed here.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal Mel-Temp. apparatus and are uncorrected. Ir spectra (KBr pellets) were run on a Perkin-Elmer 577 spectrophotometer. ^{1}H-Nmr spectra were recorded on a Bruker WM-80 spectrometer for solutions in $CDCl_3$ with TMS as an internal standard. Electron impact mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Optical rotations were taken on a Perkin Elmer 141 polarimeter for solutions in $CHCl_3$. Elemental analyses were carried out by M. H. W. Laboratories, Arizona, U. S. A., and by Butterworth Laboratories Ltd., Middlesex, England.

Methyl N-benzylglycinate and the methyl ester hydrochlorides of L-serine, L-methionine, and L-histidine were purchased from Aldrich. The rest of α-amino ester hydrochlorides used in this study were prepared from the respective α-amino acids by treating a suspension of the latter, in methanol, with thionyl chloride following literature procedure.[30] Unless otherwise

stated, the chiral α-amino acids and esters are of the L-configuration (Biochemical grade, Aldrich) and were used as received. $Eu(hfc)_3$ was purchased from Aldrich.

Preparation of 1-Arylhydrazono-1-chloroacetone Ia-k (Table 1).

(i) The particular arylamine (0.1 mol) was dissolved in cold aqueous hydrochloric acid (80 ml, 5N). To this solution was added, dropwise, a solution of sodium nitrite (7.6 g, 0.11 mol) in water (25 ml) with efficient stirring at 0-5°C. Stirring was continued for 20-30 min and the resulting fresh cold arenediazonium chloride solution was used immediately as such for the following coupling step.

(ii) A cold (-5°C), freshly prepared solution of the particular arenediazonium chloride (0.1 mol) was poured onto a cooled solution (-8°C, ice-salt bath) of α-chloroacetylacetone (13.5 g, 0.1 mol) in pyridine/water (140 ml, 1:1 v/v) with vigorous stirring. Stirring of the resulting yellow mixture was continued until a solid precipitate was formed (5-10 min). The reaction mixture was then diluted with cold water (300 ml), the solid product was collected, washed several times with cold water, dried, and recrystallized from the appropriate solvent. Yields were in the range of 80-95%.

Preparation of Methyl 2-Arylhydrazono-2-chloroacetates (IbM and jM).

These compounds were similarly prepared from the respective arenediazonium chloride and methyl α-chloroacetoacetate, as described above for Ia-k.

Preparation of 2-Phenylhydrazono-2-chloroacetophenone (IaB).

A fresh, ice-cold solution of benzenediazonium chloride (0.1 mol) was poured onto a cold solution (-8°C) of phenacyl chloride (15.5 g, 0.1 mol) in pyridine/ethanol (100 ml, 1:1 v/v) with vigorous stirring. Stirring was continued at 0-5°C for 3 h. The reaction mixture was then diluted with water (200 ml), the precipitated product was collected, washed several times with water, and recrystallized from chloroform/pet. ether (bp 40-60°C).

Preparation of α-Amino Acid Methyl Ester Hydrochlorides (III).

The following literature[30] procedure was adopted: Thionyl chloride (20 ml, 0.27 mol) was dropwise added to the particular α-amino acid (0.1 mol) in

absolute methanol (100 ml) at -5°C. The mixture was then stirred at room temperature until a clear solution was obtained (8-12 h). In the case of (±)-indoline-2-carboxylic acid, (±)-isoquinoline-3-carboxylic acid , and L-tryptophane, the reaction mixture was refluxed (12-24 h) to obtain a clear solution. The solvent was then removed under reduced pressure, the resulting solid product was collected, dried, and recrystallized from methanol/ ether. Yields were in the range 75-90%.

β -Alanine methyl ester hydrochloride was similarly prepared as above.

Preparation of 4,5-Dihydro-1,2,4-triazin-6-ones (IV; 1-23) (Table 2). To a solution of the appropriate hydrazonoyl chloride (0.02 mol) in chloroform (40 ml), or tetrahydrofuran (60 ml) was added a solution of the particular α-amino ester hydrochloride (0.02 mol) in methanol (40 ml). Triethylamine (14ml, 0.1 mol) in methanol (10 ml) was then dropwise added to the stirred mixture at 0°C. Stirring was continued at 0°C for 2-4 h, and then at ambient temperature for 10-12 h. The solvent was then removed in vacuo, and the residue was washed with water (15 ml). The resulting crude solid product was then collected and recrystallized from aqueous ethanol. Compounds (12d) and (14d) were further purified on preparative silica gel tlc plates, eluting with $CHCl_3$/EtOH (95:5 v/v).

Preparation of 3-Acetyl-1,5-diphenyl-1,2,4-triazin-6-one (V; 24a)(Table 4). A procedure, similar to that described for the oxidation of closely related 4,5-dihydro-1,2,4-triazin-6-one[23] was adopted here. Thus, to a stirred solution of 3-acetyl-1,5-diphenyl-4,5-dihydro-1,2,4-triazin-6-one (10a)(1.0 g, 3.4 mmol) in anhydrous acetone (50 ml) containing glacial acetic acid (0.6 ml, 12.0 mmol) was added, at 0°C, potassium permanganate (0.7 g, 4.4 mmol) all at once. The resulting mixture was stirred for 1 h at 0°C, filtered, and the solvent was then removed in vacuo. The residual yellow solid was recrystallized from chloroform/pet. ether. The corresponding N_1-p-nitrophenyl analogue (V; 24jM) was similarly prepared by $KMnO_4$ oxidation of the respective parent 4,5-dihydro compound (IV; 10jM).

Preparation of Compounds (VI; 25d and e)(Table 4). These compounds were

obtained from the reaction of the appropriate hyrazonoyl chloride (0.02 mol) and β-alanine methyl ester hydrochloride (0.02 mol). The procedure and experimental conditions employed here are similar to those described above for compounds (IV;1-23). The desired products were purified by recrystallization from aqueous ethanol.

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