Heterocyclization of Acetamidrazones. I. Synthesis of 1,2,4-Triazolo[4,3-*a*]pyridines *via* Ring Closure of 6-(2-Acylhydrazino)pyridine Intermediates

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The reaction of N^1-acyl-2-ethoxycarbonylacetamidrazones with ethyl ethoxymethylenecyanoacetate (EMCA) has been examined. The acetamidrazone **1a** reacts with EMCA in boiling dimethyl sulphoxide to give the 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one **2** in excellent yield. Similarly from the amidrazones **1b-h** the 1,2,4-triazolo[4,3-*a*]pyridines **3b-h** were obtained. When the reaction between the amidrazones and EMCA was performed in ethanolic solution, the 6-(2-acylhydrazino)-pyridines **4** were isolated. Ring closure of **4** afforded the 1,2,4-triazolo[4,3-*a*]pyridines.

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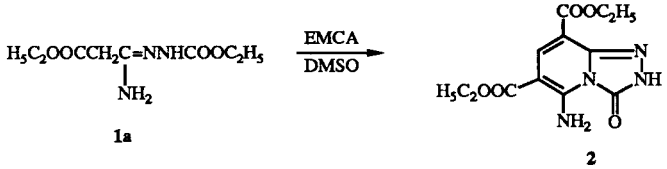
The 6,5-fused nitrogen heterocycles with a bridgehead nitrogen [1] are compounds with very interesting biological properties. Particularly the triazolo[4,3-*a*]pyridine system, to which trazodone belongs, shows significant anxiolitic properties [2]. The commonly used method of synthesis in the preparation of these systems requires condensation of 2-hydrazinopyridines with triethyl orthoformates or triethyl orthoacetates. The required 2-hydrazinopyridines are usually obtained from the 2-chloropyridines by nucleophilic displacement by hydrazine of the 2-chloro group. The synthesis of 1,2,4-triazole[4,3-*a*]-pyridine substituted on the pyridine ring is conditioned by the accessibility to the substituted 2-chloropyridine. For this reason we should have a method for the direct synthesis of these systems. This paper reports a new procedure for the preparation of 1,2,4-triazolo[4,3-*a*]pyridine derivatives by reaction of the N^1-acylacetamidrazones **1** with ethyl ethoxymethylenecyanoacetate (EMCA). By refluxing equimolecular amounts of N^1-ethoxycarbonylacetamidrazone **1a** with EMCA in dimethyl sulphoxide for 10 minutes, the 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one **2** was obtained in excellent yield (Scheme 1).

Scheme 1



1a **2**

Analogously the N^1-acylacetamidrazones **1b-h** react with EMCA in dimethyl sulphoxide/toluene 2:1 (v/v) to form the 1,2,4-triazolo[4,3-*a*]pyridine derivatives **3** (Scheme 2).

The structures of compounds **2** and **3** were determined by direct examination of the ir and ^{1}H nmr spectra (Table 2). These compounds were characterized at ir by two strong absorption bands in the region between 3460-3360 and 3360-3240, typical of the NH_2 group and by the bands of the ester group at 1695-1675 cm^{-1}. The ^{1}H nmr spectra show a broad singlet in the 8.70-8.50 ppm field, which disappears upon addition of deuterium oxide. The H-7 proton appears as a sharp singlet at 8.58-8.42 ppm.

Scheme 2

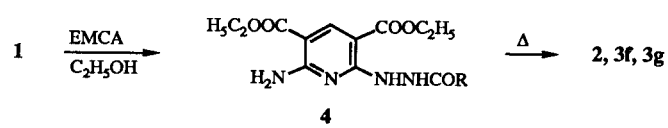
1 **3**

b, R = CH_3
c, R = $(CH_3)_2CH$
d, R = $C_6H_5CH_2$
e, R = 4-$ClC_6H_4CH_2$
f, R = C_6H_5
g, R = 4-$NO_2C_6H_4$
h, R = 4-pyridinyl

In order to clarify the trend of the reaction, the amidrazones **1** and EMCA were reacted at different conditions.

By reacting amidrazone **1a** and EMCA in ethanol at room temperature, a product with the same mp as compound **2** was obtained, but with a different Rf on testing in tlc. From an examination of the analytical and spectral results obtained the compound was characterized as diethyl 2-amino-6-(2-ethoxycarbonylhydrazino)-3,5-pyridinedicarboxylate (**4a**). Analogously the amidrazones **1f** and **1g** lead to the derivatives **4f** and **4g** respectively. The same compounds **4** were obtained if the reaction was catalysed with acetic acid.

Scheme 3



4

a, R = OC_2H_5
f, R = C_6H_5
g, R = 4-$NO_2C_6H_4$

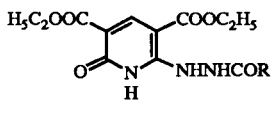
Table 1
Physical and Analytical Data of Compouns 3

Compound	R	Yield (%)	Mp (°C)	Crystallization solvent	Formula	Analysis % Calcd./Found C	H	N
3b	CH_3	86	148	acetonitrile	$C_{13}H_{16}N_4O_4$	53.42	5.52	19.17
						53.48	5.50	19.20
3c	$(CH_3)_2CH$	70	120	cyclohexane	$C_{15}H_{20}N_4O_4$	56.24	6.29	17.49
						56.29	6.27	17.45
3d	$C_6H_5CH_2$	84	150	ethanol	$C_{19}H_{20}N_4O_4$	61.94	5.47	15.21
						62.01	5.46	15.24
3e	$4\text{-}ClC_6H_4CH_2$	82	195	ethoxyethanol	$C_{19}H_{19}ClN_4O_4$	56.64	4.75	13.90
						56.62	4.74	13.86
3f	C_6H_5	88	203	ethoxyethanol	$C_{18}H_{18}N_4O_4$	61.01	5.12	15.81
						61.07	5.11	15.78
3g	$4\text{-}NO_2C_6H_4$	67	230	ethoxyethanol	$C_{18}H_{17}N_5O_6$	54.13	4.29	17.54
						54.07	4.30	17.50
3h	4-pyridinyl	76	230	ethanol	$C_{17}H_{17}N_5O_4$	57.46	4.82	19.71
						57.40	4.80	19.75

Table 2
Spectroscopic Data of Compounds 3

Compound	IR (cm^{-1})	^1H-NMR δ (ppm)
3b	3380, 3270, 1725, 1620, 1600	1.25 (t, 6H, $2CH_3$), 2.44 (s, 3H, CH_3), 4.25 (q, 4H, $2CH_2$), 8.44 (s, 1H, H-7), 8.52 (br s, 2H, NH_2)
3c	3410, 3300, 1690, 1620, 1595	1.26 (t, 3H, CH_3), 1.35 (d, 6H, $2CH_3$), 3.20 (m, 1H, CH), 4.30 (q, 2H, CH_2), 8.47 (s, 1H, H-7), 8.55 (s, 2H, NH_2)
3d	3420, 3270, 1725, 1625, 1590	1.25 (t, 3H, CH_3), 1.28 (t, 3H, CH_3), 4.18 (s, 2H, CH_2), 4.25 (m, 4H, $2CH_2$), 7.28 (m, 5H, Ar), 8.50 (s, 1H, H-7), 8.60 (br s, 2H, NH_2)
3e	3420, 3290, 1710, 1685, 1620 1590	1.26 (t, 3H, CH_3), 1.28 (t, 3H, CH_3), 4.18 (s, 2H, CH_2), 4.30 (m, 4H, $2CH_2$), 7.32 (s, 4H, Ar), 8.50 (s, 1H, H-7), 8.65 (br s, 2H, NH_2)
3f	3410, 3280, 1685, 1625, 1600 1560	1.30 (t, 6H, $2CH_3$), 4.30 (q, 4H, $2CH_2$), 7.40-7.68 (m, 3H, Ar), 8.10-8.38 (m, 2H, Ar), 8.55 (s, 1H, H-7), 8.70 (br s, 2H, NH_2)
3g	3400, 3360, 3290, 1730, 1680 1645	1.29 (t, 6H, $2CH_3$), 4.30 (q, 2H, $2CH_2$), 8.20 (d, 4H, Ar), 8.42 (s, 1H, H-7), 8.70 (br s, 2H, NH_2)
3h	3360, 3240, 1705, 1675, 1620 1590	1.32 (t, 6H, $2CH_3$), 4.31 (q, 4H, $2CH_2$), 8.06 (m, 2H, Py), 8.58 (s, 1H, H-7), 8.75 (m, 4H, 2H, Py, NH_2)

The reactions between the other amidrazones considered and EMCA still lead to the derivatives **3**. In the reaction between the amidrazones **1b** and **1e** and enol ether, besides the respective derivatives **3**, small amounts of 2-pyridones **5b** and **5e** were isolated respectively.



5b, 5e

The ^1H nmr spectra of the compounds **4** are characterised by the presence of four protons exchangeable with deuterium oxide: two singlets, one resonating at 8.30-7.90 ppm, while the other resonates at lower fields (8.98-8.70) attributable to the NH_2 and NHNHCOR groups respectively. The compound **4g** was rapidly transformed into **3g** by brief heating in ethanol, while the compounds **4a** and **4f** were transformed into their respective bicondensed derivatives **2** and **3f** by prolonged heating in dimethyl sulphoxide.

Most likely the compounds **2** and **3** are formed by nucleophilic attack of EMCA on the methylene of amidrazone, with formation of a dienamino ester analogously as shown for the reaction between the enol ethers and the analogous acetamidines [3]. Subsequently the dienamino ester undergoes an intramolecular cyclization leading to

Table 3
Experimental Results from Reaction of Amidrazones 1 and EMCA in Ethanolic Solution

Amidrazone	Catalyst used	Reaction temperature	Reaction time (hours)	Products isolated (Yield %)
1a	none	reflux	3	**4a** (65)
1a	none	room temperature	24	**4a** (74)
1a	acetic acid	room temperature	12	**4a** (41)
1b	none	reflux	3	**3b** (79), **5b** (7)
1b	none	room temperature	10	**3b** (57), **5b** (7)
1b	acetic acid	room temperature	24	**3b** (27), **5b** (6)
1c	none	room temperature	1	**3c** (84)
1c	acetic acid	room temperature	3	**3c** (73)
1d	none	reflux	15	**3d** (50)
1d	acetic acid	reflux	2	**3d** (60)
1e	none	reflux	20	**3e** (52), **5e** (5)
1e	acetic acid	reflux	12	**3e** (47)
1f	none	reflux	1	**3f** (60)
1f	none	room temperature	10	**3f** (76)
1f	acetic acid	room temperature	1	**4f** (60)
1g	none	room temperature	120	**4g** (58)
1g	none	reflux	2	**3g** (54)
1g	acetic acid	room temperature	120	**4g** (53)
1h	none	reflux	8	**3h** (37)
1h	none	room temperature	48	**3h** (20)
1h	acetic acid	reflux	13	**3h** (31)

the pyridine derivative **4** where a further cyclization between amidic CO and pyridinic nitrogen occurs.

EXPERIMENTAL

The melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in nujol with a Perkin-Elmer 325 spectrophotometer. The ^{1}H nmr spectra were recorded for hexadeuteriodimethyl sulphoxide solution with a Varian FT 80 spectrometer; chemical shifts are reported in ppm from HMS as an internal standard and are given in δ units. The elemental analyses (C,H,N) were carried out with a Carlo Erba model 1106 Elemental Analyzer. The reaction mixture was monitored by tlc on DC-Alufolien kieselgel $60F_{254}$ (Merck). The N^1-acyl-2-ethoxycarbonylacetamidrazones **1** were obtained with a previously described procedure [4].

N^1-Isobutyryl-2-ethoxycarbonylacetamidrazone (**1c**).

A mixture of ethyl 3-ethoxy-3-iminopropionate (10 mmoles) and isobutyrylhydrazine (10 mmoles) in 50 ml of anhydrous ethanol was heated at 70° for 2 minutes and stirred at room temperature for 4 hours. The formed precipitate was collected by filtration and thouroughly washed in ethyl ether, mp 130° (from acetonitrile), yield 80%; ir (nujol): 3460, 3380, 3300, 1745, 1725, 1680, 1665 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.10 (m, 9H, $3CH_3$), 2.30 (m, 1H, CH), 3.03 (s, 1H, =CH), 4.03 (q, 2H, CH_2), 6.10 (s, 2H, NH_2), 9.18 (s, 1H, NH), 9.28 (s, 1H, NH).

Anal. Calcd. for $C_9H_{17}N_3O_3$: C, 50.22; H, 7.96; N, 19.52. Found: C, 50.25; H, 7.94; N, 19.49.

5-Amino-6,8-[bis(ethoxycarbonyl)]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one (**2**).

A solution of acetamidrazone **1a** (10 mmoles) in dimethyl sulphoxide (10 ml) was treated with ethyl ethoxymethylenecyanoacetate (10 mmoles) and the mixture was heated under reflux for 10 minutes. The reaction mixture was cooled, poured into water (50 ml) and the solid thus obtained was crystallized from ethoxyethanol to give **2** (86%), mp 295° dec; ir (nujol): 3430, 3305, 1720, 1695, 1665, 1640, cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.25 (t, 3H, CH_3), 1.28 (t, 3H, CH_3), 4.32 (m, 4H, $2CH_2$), 8.42 (s, 1H, H-7).

Anal. Calcd. for $C_{12}H_{14}N_4O_5$: C, 48.98; H, 4.80; N, 19.04. Found: C, 49.02; H, 4.82; N, 19.00.

1,2,4-Triazolo[4,3-*a*]pyridine Derivatives **3**. General Procedure.

Method A.

A solution of **1b-h** (10 mmoles) and ethyl ethoxymethylenecyanoacetate (10 mmoles) in dimethyl sulphoxide/toluene 2:1 (v/v) (ml 15) was refluxed for 30 minutes. The toluene was evaporated at reduced pressure and 50 ml of water was added. The solid was collected by filtration and was crystallized to give the compounds **3**. The yield for compounds **3** is reported in Table 1.

Method B.

A solution of amidrazone **1** (10 mmoles) and EMCA (10 mmoles) in anhydrous ethanol (50 ml) was stirred at the temperature and for the time reported in Table 3. The resulting compounds were isolated by crystallization of the formed precipitate or by evaporation under reduced pressure and trituration of the residue with ethyl acetate.

Ethyl 6-(2-Acetylhydrazino)-3-cyano-1,2-dihydro-2-oxo-5-pyridinecarboxylate (**5b**).

The pyridone **5b** was isolated as a collateral product from the reaction of amidrazone **1b** with EMCA. After removal of the ethanol, the residue was treated with ethyl acetate to dissolve the compound **3b**. The insoluble solid was collected by filtration and crystallized from ethanol to give **5b**, mp 230°; ir (nujol): 3240, 3170, 2220, 1675, 1655 cm^{-1}, ^{1}H nmr (DMSO-d_6): δ 1.24 (t, 3H,

CH_3), 2.02 (s, 3H, CH_3), 4.14 (q, 2H, CH_2), 8.26 (s, 1H, H-4), 8.82 (s, 2H, NHNHCO), 10.65 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.07; H, 4.56; N, 21.17.

Ethyl 6-[2-(4-Chlorophenylacetyl)hydrazino]-3-cyano-1,2-dihydro-2-oxo-5-pyridinecarboxylate (**5e**).

The pyridone **5e** was isolated as a collateral product from the reaction of amidrazone **1e** with EMCA. After cooling, the resulting precipitate was collected by filtration, crystallized and identified as **3e**. The filtrate was evaporated *in vacuo* to give another solid which was crystallized from acetonitrile and identified as **5e**, mp 210°; ir (nujol): 3360, 3250, 2220, 1720, 1700, 1665 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_3), 3.70 (s, 2H, CH_2), 4.15 (q, 2H, CH_2), 7.32 (m, 4H, Ar), 8.28 (s, 1H, H-4), 9.00 (br s, 3H, 3NH).

Anal. Calcd. for $C_{17}H_{15}ClN_4O_4$: C, 54.48; H, 4.03; N, 14.95. Found: C, 54.52; H, 4.01; N, 15.00.

Method C.

To a solution of amidrazone **1** (10 mmoles) in anhydrous ethanol (50 ml), EMCA (10 mmoles) and acetic acid (1 ml) were added. The mixture was stirred at the temperature and for the time reported in Table 3. After concentration, the residue was poured into water (50 ml) and neutralized with 20% sodium hydroxide. The precipitate thus obtained was filtered off and crystallized from the appropriate solvent to give the products reported in Table 3.

Diethyl 2-Amino-6-(2-ethoxycarbonylhydrazino)-3,5-pyridinedicarboxylate (**4a**).

A mixture of **1a** (10 mmoles), EMCA (10 mmoles) and acetic acid (1 ml) was stirred for 3 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was poured in 50 ml of water and neutralized. The precipitate was collected by filtration and washed with water. This crude product was recrystallized from acetonitrile to give **4a**, mp 295° in 41% yield; ir (nujol): 3400, 3380, 1680, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.25 (t, 9H, $3CH_3$), 3.98 (q, 2H, CH_2), 4.28 (q, 4H, 2 CH_2), 8.30 (br s, 2H, NH_2), 8.48 (s, 1H, H-4), 8.70 (br s, 2H, NHNHCO).

Anal. Calcd. for $C_{14}H_{20}N_4O_6$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.45; H, 5.90; N, 16.40.

Diethyl 2-Amino-6-(2-benzoylhydrazino)-3,5-pyridinedicarboxylate (**4f**).

This compound was synthesized in 60% yield in a similar way to that described for the preparation of **4a**. The compound **4f** was crystallized from acetonitrile, mp 187°; ir (nujol): 3430, 3320, 3150, 1680, 1645 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.27 (t, 6H, $2CH_3$), 4.30 (q, 4H, $2CH_2$), 7.40 (m, 3H, Ar), 7.90 (br s, 2H, NH_2), 8.00 (m, 2H, Ar), 8.57 (s, 1H, H-4), 8.67 (br s, 2H, NHNHCO).

Anal. Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41; N, 15.05. Found: C, 58.00; H, 5.40; N, 15.09.

Diethyl 2-Amino-6-[2-(4-nitrobenzoyl)hydrazino]-3,5-pyridinedicarboxylate (**4g**).

This compound was synthesized in 53% yield in a similar way to that described for the preparation of **4a**. This compound was purified by silica gel column chromatography (ethyl acetate/propanol 4:1); mp 180°; ir (nujol): 3350, 3280, 1735, 1680, 1625 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.17 (t, 3H, CH_3), 1.27 (t, 3H, CH_3), 4.05 (q, 2H, CH_2), 4.15 (q, 2H, CH_2), 8.22 (m, 6H, Ar + NH_2), 8.60 (s, 1H, H-4), 8.70 (br s, 2H, NHNHCO).

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.59; N, 16.78. Found: C, 51.75; H, 4.56; N, 16.75.

Ring Closure of **4a**, **4f** and **4g**.

A solution of **4a** (5 mmoles) in dimethyl sulphoxide (10 ml) was refluxed for 10 hours. The reaction mixture was then worked up as described above (Method A) to give **2**, mp 295° in 85% yield.

Following the above procedure, the compound **4f** was transformed to **3f** in 80% yield.

The solution of **4g** (5 mmoles) in ethanol (10 ml) was refluxed for 5 minutes and then evaporated under reduced pressure. The resulting residue was crystallized to give **3g** in 95% yield.

Acknowledgements.

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