1,2,3-Triazolo[1,5-*a*]quinolines, -[1,7]naphthyridines, and -benzo[1,5]diazepines by the Action of Diethyl 1,3-Acetonedicarboxylate Anion on *ortho*-Substituted Aryl Azides

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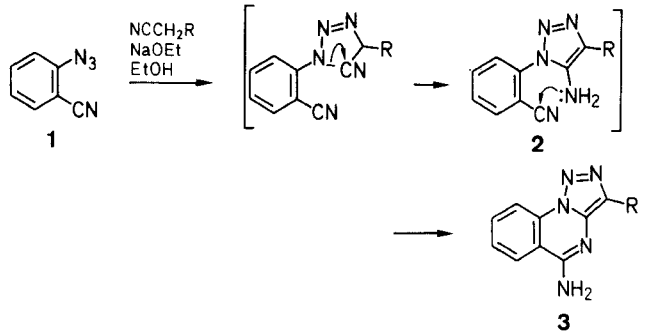
The title compounds were prepared by the action of the diethyl 1,3-acetonedicarboxylate anion on *ortho*-substituted aryl azides. The anion was formed using either a sodium alkoxide in the appropriate alcohol or by an ion-exchange resin [Amberlite IRA-400(OH)].

The synthesis of 1,2,3-triazoles by the action of carbanions on aryl azides is well-known,[1,2] and the method has been extended recently to heterocyclic azides.[3,4] Of particular interest are the reactions of cyano-substituted carbanions (RCHCN; R = CO_2Et, Ph, $CONH_2$, CN) with aryl azides bearing an electrophilic *ortho* substituent (e.g. NO_2, CN, or CO_2H). In such cases, intramolecular cyclisation of the amino group of the initially formed 5-amino-1-aryl-1,2,3-triazole **2** onto the electrophilic centre yields a tricyclic product **3** as exemplified in Scheme **A**.



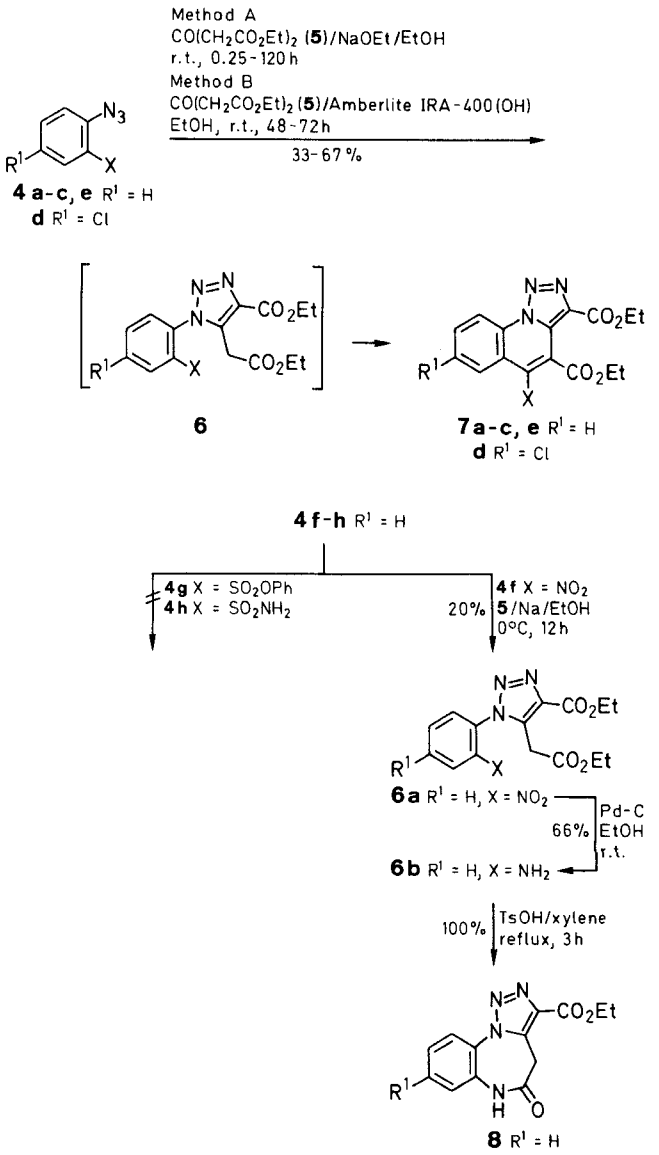
Scheme **A**

We report herein a variation of this simple and effective cyclisation procedure using diethyl 1,3-acetonedicarboxylate (diethyl 3-oxopentanedioate) as the carbanion source which gives useful preparative routes to new derivatives of the little known[6] 1,2,3-triazolo[1,5-*a*]quinoline system, new tricyclic 1,2,3-triazolonaphthyridines and a novel triazolobenzo[1,5]diazepine.

Treatment of *o*-azidobenzonitrile **4a** with the acetonedicarboxylate **5** in the presence of sodium ethoxide gave diethyl 6-amino-1,2,3-triazolo[1,5-*a*]quinoline-4,5-dicarboxylate (**7a**) in 64% yield. Presumably, reaction proceeds *via* an intermediate 1,2,3-triazole **6** (Scheme **B**) which was isolated only in the case of the nitro azide (**4f**; see later).

Likewise, base-catalysed (NaOR in ROH, or basic ion-exchange resin) condensation of **5** with *o*-azidoacetophenone (**4b**), *o*-azidobenzaldehyde (**4c**), 2-azido-5-chlorobenzophenone (**4d**), and with methyl *o*-azidobenzoate (**4e**) gave the 1,2,3-triazolo[1,5-*a*]quinoline-4,5-dicarboxylates **7b–e** (Scheme **B**).

3-Azido-4-cyanopyridine (**9a**) and ethyl 3-azidopyridine-4-carboxylate (**9b**) behaved similarly with **5** to produce the amino-1,2,3-triazolo[1,5-*a*][1,7]naphthyridine **10a** and the hydroxy derivative **10b**, respectively. As far as we are aware these represent the first derivatives of this hitherto unreported heterocyclic system.



4, 6	X	7	R^1
a	CN	**a**	NH_2
b	COMe	**b**	Me
c	CHO	**c**	H
d	COPh	**d**	Ph
e	CO_2Me	**e**	OH

Scheme **B**

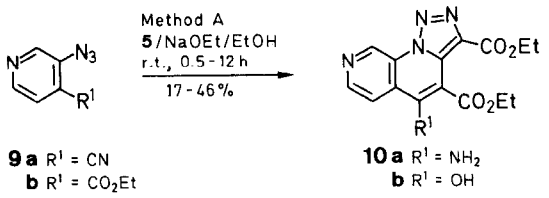


Table. 1,2,3-Triazolo[1,5-*a*]quinolines (**7a–e**) and 1,2,3-Triazolo[1,7]naphthyridines (**10a,b**)

Product	Method (Reaction Time h)	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	IR (Nujol)[d] ν(cm^{-1})	^{1}H-NMR[e] ($CDCl_3$/TMS)[f] δ, J(Hz)[g]	MS (70eV)[h] *m/z* (%)
7a	A (0.5)	67	189	$C_{16}H_{16}N_4O_4$ (328.3)	3403, 3304, 3217 (NH_2), 1731, 1696 (2 × C=O)	1.4 (t, 3H, CH_3), 1.24 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 4.4 (q, 2H, CH_2), 6.85 (br s, 2H, NH_2), 7.78–7.83 (m, 2H$_{arom}$), 7.57–7.63 (m, 1H$_{arom}$), 8.75 (dd, 1H$_{arom}$)	328 (M^+, 4.6), 300 (27), 171 (100)
7b	B (72)	35	122	$C_{17}H_{17}N_3O_4$ (327.3)	1740, 1715 (2 × C=O)	1.43 (t, 3H, CH_3), 1.36 (t, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.46 (q, 2H, CH_2), 4.5 (q, 2H, CH_2), 7.65–7.7 (m, 1H$_{arom}$), 7.79–7.85 (m, 1H$_{arom}$), 8.03 (dd, 1H$_{arom}$), 8.86 (m, 1H)	299 ($M^+ - 28$, 25)[i], 142 (100)
7c	B (48)	35	102 (dec)	$C_{16}H_{15}N_3O_4$ (313.3)	1729 (br s) (2 × C=O)	1.33 (t, 3H, CH_3), 1.40 (t, 3H, CH_3), 4.40 (q, 2H, CH_2), 4.44 (q, 2H, CH_2), 7.6–7.65 (m, 1H$_{arom}$), 7.8–7.9 (m, 1H$_{arom}$), 8.06 (s, 1H, CH), 8.78 (d, 1H$_{arom}$)	285 ($M^+ - 28$, 14)[i], 128 (100)
7d	A (12)	40	244	$C_{22}H_{18}ClN_3O_4$ (422.85)	1745, 1720 (2 × C=O)	0.98 (t, 3H, CH_3), 1.40 (t, 3H, CH_3), 4.40 (q, 2H, CH_2), 4.45 (q, 2H, CH_2), 7.34–7.53 (m, 6H$_{arom}$), 7.78 (dd, 1H$_{arom}$), 8.86 (dd, 1H$_{arom}$)	423 (M^+, 4), 395 (43.5), 238 (100)
7e	A (120)	33	110	$C_{16}H_{15}N_3O_5$ (329.3)	3306 (OH), 1733, 1662 (2 × C=O)	1.44 (t, 3H, CH_3), 1.36 (t, 3H, CH_3), 4.44 (q, 2H, CH_2), 4.45 (q, 2H, CH_2), 7.64–7.69 (m, 1H$_{arom}$), 7.87–7.93 (m, 1H$_{arom}$), 8.33 (d, 1H$_{arom}$), 8.74 (d, 1H$_{arom}$), 12.63 (br s, 1H, OH)	329 (M^+, 4.5), 301 (14), 144 (100)
10a	A (0.25)	46	230 (dec)	$C_{15}H_{15}N_5O_4$ (329.3)	3305, 3200 (NH_2), 1696, 1626 (2 × C=O)	0.99 (t, 3H, CH_3), 1.13 (t, 3H, CH_3), 4.02 (q, 2H, CH_2), 4.11 (q, 2H, CH_2), 7.73 (br s, 2H, NH_2), 8.04 (d, 1H$_{arom}$), 8.56 (d, 1H$_{arom}$), 10.13 (d, 1H$_{arom}$)	301 ($M^+ - 28$, 12)[i], 144 (100)
10b	A (12)	17	115	$C_{15}H_{14}N_4O_5$ (330.3)	3150 (OH), 1729, 1670 (2 × C=O)	1.37 (t, 3H, CH_3), 1.44 (t, 3H, CH_3), 4.46 (q, 2H, CH_2), 4.47 (q, 2H, CH_2), 8.15 (d, 1H$_{arom}$), 8.93 (d, 1H$_{arom}$), 10.13 (s, 1H$_{arom}$), 12.5 (br s, 1H, OH)	330 (M^+, 3), 302 (14.7), 145 (100)

[a] Yield of pure product – yields not optimised.
[b] Uncorrected.
[c] Satisfactory microanalysis obtained: C ±0.3, H ±0.25, N ±0.2. Except **7c** C +0.6, H +0.1, N +0.7.
[d] Recorded on a Perkin-Elmer 1710 Fourier Transform Infrared Spectrometer.
[e] Obtained on a Brucker AC 300 MHz NMR spectrometer.
[f] Except **10a** which was obtained in $CDCl_3$/DMSO-d_6.
[g] For $-CH_2CH_3$ J = 7.1–7.37 Hz in all cases.
[h] Recorded on a Finnegan 4000 mass spectrometer.
[i] Products probably decompose by loss of N_2 from a diazo intermediate of the type involved in the Dimroth rearrangement.[11]

As expected, the reaction of diester **5** with *o*-nitrophenyl azide **4f** in the presence of sodium ethoxide gave ethyl 4-(ethoxycarbonyl)-1-(*o*-nitrophenyl)-1,2,3-triazole-5-acetate (**6a**), albeit in poor yield (20%). Catalytic reduction using hydrogen and palladium on charcoal furnished the amine **6b** which, on heating in xylene in the presence of a catalytic amount of *para*-toluenesulphonic acid, underwent cyclisation to the novel 1,2,3-triazolo[1,5-*a*]-benzo[1,5]diazepinone **8** in quantitative yield.

Attempts, so far, to effect based-catalysed cyclisations of diester **5** with *o*-azidobenzenesulphonamide (**4h**) and with phenyl *o*-azidobenzenesulphonate (**4g**), have failed, as have efforts to obtain heterocyclic systems by the action of dicarbanions on aryl azides.

o-Nitrophenyl azide, *o*-azidobenzonitrile, *o*-azidoacetophenone, methyl 2-azidobenzoate and 5-chloro-2-azidobenzophenone were prepared from the corresponding amines by azidation of the diazonium salts, as described previously.[7] Ethyl 3-azidopyridine-4-carboxylate (oil) [ν_{max} liquid film 2130 (N_3), 1730 (CO_2R), cm^{-1}] was prepared (57.6% yield) similarly from ethyl 3-aminopyridine-4-carboxylate,[8] and was used directly without further purification. 3-Azido-4-cyanopyridine was obtained as directed[9] from the 3-chloro-4-cyano derivative, whereas *o*-azidobenzaldehyde was obtained by oxidation of *o*-azidobenzyl alcohol with pyridinium chlorochromate.[10]

1,2,3-Triazolo Systems 7a–7e, 10a, 10b; General Procedures:
Method A, (for **7a, 7d, 7e, 10a, 10b**) *Using NaOEt/EtOH:* A solution of NaOEt (1 equiv) in EtOH (20 mL) is added dropwise to an equimolar mixture of the *o*-substituted aryl azide 5 mmol and diethyl 1,3-acetonedicarboxylate 5 mmol in EtOH (50 mL). The reaction mixture is stirred at r.t. (see Table) and then filtered to yield the crude product, which is washed with H_2O, air dried and recrystallised from EtOH.

For azido ester **4e** and for ethyl 4-azidopyridine-3-carboxylate (**9b**) the residues obtained by filtration of the reaction mixtures are dissolved in H_2O (20 mL) and the solution neutralised by careful addition of 10% hydrochloric acid, whereupon the crude hydroxy-

derivatives **7e** and **10b**, respectively, are obtained. For spectroscopic data see Table. (Note – For azido ester **4e**, NaOMe/MeOH is used as the base.)

Method B, (for **7b, 7c**) *Using ion-exchange resin:* A mixture of the *o*-substituted aryl azide (4 mmol), diethyl 1,3-acetonedicarboxylate (4 mmol) and basic ion-exchange resin [Amberlite IRA-400 (OH)] (2 g) in EtOH (25 mL) is stirred for several hours (see Table) at r.t. The mixture is then heated to boiling and whilst hot filtered rapidly to remove the resin. Evaporation of the ethanolic filtrate yields the crude product which is purified by flash chromatography on silica gel; EtOAc/petroleum ether (bp 40–60 °C); (2:5 w/v) as eluent followed by crystallisation from EtOH. For spectroscopic data see Table.

Ethyl 4-(Ethoxycarbonyl)-1-(*o*-nitrophenyl)-1,2,3-triazole-5-acetate (6a):

A solution of Na (0.7 g; 30.4 mmol) in EtOH (50 mL) is added in one-portion to an ice-cooled solution of *o*-nitrophenyl azide (5 g; 30.4 mmol) and diethyl 1,3-acetonedicarboxylate (5.54 mL; 30.4 mmol) in EtOH (100 mL). The mixture is stirred overnight and then the solvent evaporated, under vacuum, to low volume (ca. 20 mL). The concentrated EtOH solution is then poured into cold H_2O (100 mL) and extracted with Et_2O (3 × 25 mL). The Et_2O extracts are dried ($MgSO_4$) and evaporated to yield the crude product which is purified by flash chromatography on silica gel; [EtOAc/petroleum ether (bp 60–80 °C), 3:7] as eluent. **6a** is obtained as a white solid; yield: 2.1 g (20%); mp 78–79 °C (EtOH).

$C_{15}H_{16}N_4O_6$	calc.	C 51.74	H 4.47	N 16.20
(348.3)	found	51.72	4.63	16.08

MS (DEI): *m/z* (%) = 348 (M^+, 9), 99 (100).

IR (Nujol): ν = 1738 (b) cm^{-1} (2 × C=O).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, 3 H, 7.13 Hz, CH_3), 1.44 (t, 3 H, 7.13 Hz, CH_3), 3.97 (s, 2 H, CH_2), 4.09 (q, 2 H, 7.13 Hz, CH_2), 4.44 (q, 2 H, 7.13 Hz, CH_2), 7.59–7.62 (dd, 1 H_{arom}), 7.77–7.85 (m, 2 H_{arom}), 8.19–8.22 (dd, 1 H_{arom}).

Ethyl 1-(*o*-Aminophenyl)-4-ethoxycarbonyl-1,2,3-triazole-5-acetate (6b):

A solution of nitro compound **6a** (2 g; 5.7 mmol) in EtOH (100 mL) is reduced in a standard atmospheric hydrogenator with hydrogen and 5% Pd–C catalyst (0.2 g). After reduction is complete, the mixture is filtered through Celite and the filtrate evaporated to dryness. Flash chromatography on silica gel [EtOAc/petroleum ether (bp 60–80 °C) (2:3 v/v)] as eluent gives triazole **6b** as an off-white solid which crystallises from toluene: yield: 1.2 g (66%); mp 103 °C.

$C_{15}H_{18}N_4O_4$	calc.	C 56.59	H 5.69	N 17.60
(318.3)	found	56.87	5.62	18.02

MS (DEI): *m/z* (%) = 318 (M^+, 5), 143 (100).

IR (Nujol): ν = 3460, 3369, 3233 (NH_2), 1739 cm^{-1} (2 × C=O).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, 3 H, 7.14 Hz, CH_3), 1.40 (t, 3 H, 7.12 Hz, CH_3, 3.82 (s, 2 H, NH_2), 3.91 (s, 2 H, CH_2), 4.09 (q, 2 H, 7.12 Hz, CH_2), 4.42 (q, 2 H, 7.14 Hz, CH_2), 6.79–6.86 (m, 2 H_{arom}), 7.07–7.10 (dd, 1 H_{arom}), 7.24–7.32 (m, 1 H_{arom}).

4-Ethoxycarbonyl-5,6-dihydro-1,2,3-triazolo[1,5-*a*]benzo[1,5]diazepin-6(7*H*)-one (8):

The amino ester **6b** (0.4 g; 1.47 mmol) is heated under reflux for 3 h in xylene (25 mL) containing a catalytic amount (10–20 mg) of TsOH. The solution is then cooled whereupon the triazolobenzodiazepinone **8** separates as a pale-orange solid; yield: 0.35 g (100%); mp 195 °C (toluene).

$C_{13}H_{12}N_4O_3$	calc.	C 57.35	H 4.44	N 20.57
(272.3)	found	57.16	4.38	20.80

MS (DEI): *m/z* (%) = 272 (M^+, 17), 49 (100).

IR (Nujol): ν = 3240 (NH), 1700 (b) cm^{-1} (CO_2Et, CONH).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, 3 H, 7.14 Hz, CH_3), 4.15 (s, 2 H, CH_2), 4.46 (q, 2 H, 7.14 Hz, CH_2), 7.23–7.28 (m, 1 H_{arom}), 7.37–7.43 (m, 1 H_{arom}), 7.49–7.55 (m, 1 H_{arom}), 8.04–8.07 (dd, 1 H_{arom}), 8.86 (s, 1 H, NH).

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