Reactions of 3-Chloro-6-hydrazinopyridazine with Michael-retro-Michael Reagents

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Although pyrazole formation results from treatment of 3-chloro-6-hydrazinopyridazine (**2**) with both ethoxymethylenemalononitrile and ethyl (ethoxymethylene)cyanoacetate, 6-chlorotriazolo[4,3-*b*]pyridazine (**5**) was produced (75% yield) when **2** was treated with diethyl ethoxymethylenemalonate. Treatment of **2** with diethyl acetylmalonate (**8**) gave both 6-chloro-3-methyltriazolo[4,3-*b*]pyridazine (**10**) and 5-hydroxy-3-methyl-1-(6-chloro-3-pyridazinyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (**12**). Pyrazole **12** was initially isolated as a salt of triazolopyridazine **10**.

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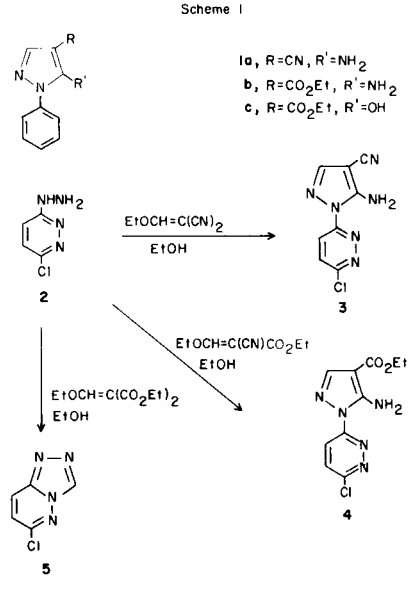
The 1-phenyl-4,5-disubstituted pyrazoles **1a, 1b** and **1c** are all known literature compounds. 5-Amino-4-cyano-1-phenylpyrazole (**1a**) was prepared from phenylhydrazine and ethoxymethylenemalononitrile (1); 5-amino-1-phenyl-4-pyrazolecarboxylic acid ethyl ester (**1b**) was prepared from phenylhydrazine and diethyl ethoxymethylenemalonate (2); and 5-hydroxy-1-phenyl-4-pyrazolecarboxylic acid ethyl ester (**1c**) has been prepared from phenylhydrazine and 1,1,3,3-tetraethoxycarbonylpropene (3,4).

We were recently interested in preparing 1-arylpyrazoles analogous to **1a-c** in which the 1-aryl substituent was 6-chloro-3-pyridazinyl. We found that pyrazoles **3** (5) and **4** (6) were known in the literature. In our preparations of **3** and **4**, treatment of 3-chloro-6-hydrazinopyridazine (**2**) with ethoxymethylenemalononitrile afforded **3** in 91% yield, and treatment of **2** with ethyl (ethoxymethylene)-cyanoacetate gave **4** in 81% yield (Scheme I). We were, therefore, surprised to find that treatment of **2** with diethyl ethoxymethylenemalonate under the same conditions produced 6-chlorotriazolo[4,3-*b*]pyridazine (**5**) in 75% yield, rather than the expected pyrazole. This transformation is not interesting from a preparative standpoint, since **5** can readily be produced from **2** with less exotic reagents (7), but it is very interesting mechanistically.

Scheme I



In Scheme II we depict a mechanism for the formation of triazolopyridazine **5** from **2** and diethyl ethoxymethylenemalonate. Intermediate **6** results from a Michael-retro-Michael interaction of the reactants. Pyrazole formation would result from **6** if the amino group attached to the pyridazine ring condensed with one of the esters. However, Michael addition of the pyridazine nitrogen to the enediester system is apparently favored, and intermediate **7** results. Subsequent elimination of diethylmalonate from intermediate **7** then produces triazolopyridazine **5**.

We were able to substantiate the mechanism shown in Scheme II by performing an experiment in which we isolated **6**. Treatment of **2** with diethyl ethoxymethylenemalonate in dimethylformamide at 75-80° for 20 minutes gave **6** in 74% yield. When we heated a solution of **6** in acetonitrile at reflux, triazolopyridazine **5** was produced in 94% yield.

Since hydrazine **6** was shown to be an intermediate in the preparation of **5** from **2** and diethyl ethoxymethylenemalonate, it is reasonable to assume that analogous intermediates are formed from **2** in the transformations of **2** to **3** and **4**. It is interesting to speculate as to why pyrazole formation results from intermediates analogous to **6** in these latter transformations, and triazolopyridazine formation results from **6**. These results *cannot* be explained on the basis of pK_a values of the three active methylene compounds which are listed in Scheme II (8). The anion of the active methylene compound with the lowest pK_a value should be the best leaving group in an intermediate

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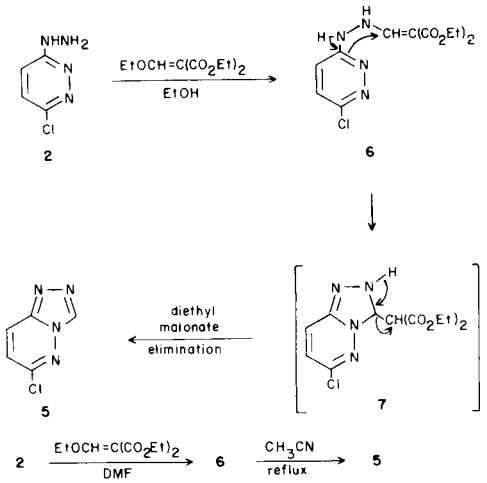
analogous to **7**. However, the pK_a of diethyl malonate is the highest of the three, and one would predict that the anions of both malononitrile and ethyl cyanoacetate would be better leaving groups. The conclusion which we draw from the interesting and divergent results in Scheme I is that condensation of an amine with a nitrile is *favored* relative to condensation of an amine with an ester.

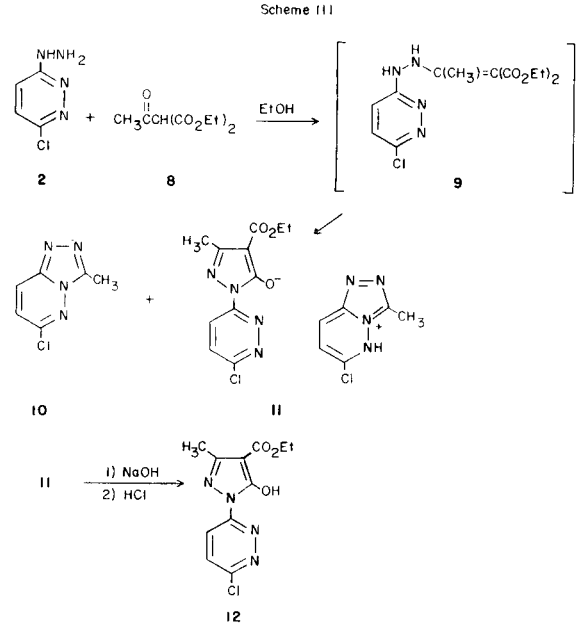
Scheme II



Compound	pK_a
$CH_2(CN)CO_2Et$	9
$CH_2(CN)_2$	11
$CH_2(CO_2Et)_2$	13

We were next interested to see whether we could alter the course of the reaction shown in Scheme II by using a diethyl malonate substrate which would favor pyrazole formation at the expense of triazolopyridazine formation. To this end, we treated **2** with diethyl acetylmalonate. We reasoned that in proposed intermediate **9** (Scheme III), the methyl group on the double bond of the enediester system should impose a steric and an electronic barrier to Michael addition of the pyridazine nitrogen to the enediester. The results of this interesting experiment indicated that we were able to change the course of the reaction to an extent, in that both 6-chloro-3-methyltriazolo[4,3-*b*]pyridazine (**10**) and 5-hydroxy-3-methyl-1-(6-chloro-3-pyridazinyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (**12**) were produced. Triazolopyridazine **10** appeared to be the major product of this reaction. Pyrazole **12** was initially isolated as a salt with **10**. (We have drawn this salt as **11**, realizing that there are other possible positions for protonation on the triazolopyridazine.) This salt (**11**) displayed a sharp melting point (181-182°), which was different from those of **10** (m.p. 106-107°) and **12** (m.p. 193-195°), and retained its integrity upon repeated recrystallization from ethanol. Pyrazole **12** was prepared from **11** (78% yield) by treating a methylene chloride solution of **11** with aqueous sodium hydroxide, which precipitated the sodium salt of **12**, followed by acidification of this sodium salt. The acidity of pyrazole **12** and its propensity to form a salt with triazolopyridazine **10** was unexpected. However, there are two available intramolecular hyrogen bonding sites for the hydroxyl hydrogen. Hydrogen bonding of the hydroxyl hydrogen with an ester oxygen or with the pyridazinyl nitrogen would both lead to six-membered (preferred) charge-delocalized species, which would weaken the oxygen-hydrogen bond. Thus, the acidity of **12** can be rationalized on the basis of hydrogen bonding.

Scheme III



EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727B Spectrophotometer, nmr spectra with a Varian EM-360A spectrometer, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Dow Analytical Laboratories and Midwest Microlab, Ltd., Indianapolis, IN.

Materials.

3-Chloro-6-hydrazinopyridazine (**2**), m.p. 135-138° [lit. (9) m.p. 135-137°] was prepared from 3,6-dichloropyridazine and hydrazine hydrate in methanol, and recrystallized from water (9). Diethyl acetylmalonate (**8**) was obtained from Chemicals Procurement Laboratories, Inc.

5-Amino-1-(6-chloro-3-pyridazinyl)-1*H*-pyrazole-4-carbonitrile (**3**).

A mixture of 14.5 g. (0.100 mole) of **2** and 13.4 g. (0.110 mole) of ethoxymethylenemalononitrile in 150 ml. of ethanol was heated to reflux. The color of the mixture changed from orange to yellow and a voluminous white solid separated. An additional 150 ml. of ethanol was added and the mixture was heated at reflux for 1 hour. The mixture was cooled and the solid was collected and oven dried to give 20.0 g. (91%) of **3**, m.p. 245-247° (methanol) (5); ir (Nujol): 3400 and 3300 (NH), 2240 (C≡N), 1630 (C=N) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.25-7.90 (m, 3H, with s, pyrazole H, 1H, at 8.06).

Anal. Calcd. for $C_8H_5ClN_6$: C, 43.55; H, 2.28; N, 38.10. Found: C, 43.50; H, 2.32; N, 38.36.

5-Amino-1-(6-chloro-3-pyridazinyl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**4**).

A solution of 28.9 g. (0.200 mole) of **2** and 37.2 g. (0.220 mole) of ethyl (ethoxymethylene)cyanoacetate in 400 ml. of ethanol was heated at reflux for 3.5 hours. After standing overnight the resulting crystals were collected and air-dried to yield 43.6 g. (81%) of **4**, m.p. 133-134° [lit. (6) m.p. 132-135°]; ir (Nujol): 3430 and 3300 (NH), 1675 (C=O), 1610 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.26 (d, J = 10 Hz, 1H, pyridazine H at 4-position), 8.05 (d, J = 10 Hz, 1H, pyridazine H at 5-position), 7.84 (s, 1H, pyrazole H), 7.59 (broad s, 2H, NH_2), 4.26 (q, J = 7.5 Hz, 2H, CH_2), 1.30 (t, J = 7.5 Hz, 3H, CH_3).

Anal. Calcd. for $C_{10}H_{10}ClN_5O_2$: C, 44.87; H, 3.76; N, 26.16. Found: C, 44.70; H, 3.75; N, 26.26.

6-Chlorotriazolo[4,3-*b*]pyridazine (**5**). A. From **2** and Diethyl Ethoxymethylenemalonate.

A solution of 8.60 g. (59.5 mmoles) of **2** and 14.1 g. (65.0 mmoles) of diethyl ethoxymethylenemalonate in 100 ml. of acetonitrile was heated at reflux for 3 hours. The solution was cooled and the resulting golden brown needles were collected and air-dried to yield 6.90 g. (75%) of **5**, m.p. 202-203° [lit. (7) m.p. 203.5°]; ir (Nujol): 1530, 1470, 1330, 1120, 1010, 945 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 9.53 (s, 1H, H at 3-position), 8.43 (d, J = 10 Hz, 1H, H at 8-position), 7.42 (d, J = 10 Hz, 1H, H at 7-position).

B. From **6**.

A solution of 5.00 g. (15.9 mmoles) of **6** in 75 ml. of acetonitrile was heated at reflux for 4 hours. The solution was concentrated to a small volume and cooled. The resulting golden brown needles were collected and air-dried to yield 2.30 g. (94%) of **5**, m.p. 203-204° [lit. (7) m.p. 203.5°]. This material was spectrally identical to that prepared in Part A.

[(2-(6-Chloro-3-pyridazinyl)hydrazino)methylene]propanedioic Acid Diethyl Ester (**6**).

A solution of 7.22 g. (50.0 mmoles) of **2** and 11.8 g. (55.0 mmoles) of diethyl ethoxymethylenemalonate in 25 ml. of dimethylformamide was heated at 75-80° for 20 minutes. The warm solution was diluted with water and cooled. The resulting white, crystalline solid was collected and air-dried to yield 11.6 g. (74%) of **6**; m.p. 165° (ethanol-water); ir (Nujol): 3200 (NH), 1680 (C=O), 1650, 1615 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.5-9.7 (broad signal, 2H, both NH groups), 8.08-7.87 (m, 1, C=CH), 7.65 (d, J = 9 Hz, 1H, pyridazine H at 5-position), 7.12 (d, J = 9 Hz, 1H, pyridazine H at 4-position), 4.38-3.93 (m, 4H, both CH_2 groups), 1.22 (t, J = 7.5 Hz, 6H, both CH_3 groups); ms: (70 eV, electron impact) m/e 314 (molecular ion).

Anal. Calcd. for $C_{12}H_{15}ClN_4O_4$: C, 45.79; H, 4.80; N, 17.80. Found: C, 45.96; H, 4.85; N, 17.43.

Treatment of **2** with Diethyl Acetylmalonate.

A solution of 7.23 g. (50.0 mmoles) of **2** and 10.1 g. (50.0 mmoles) of diethyl acetylmalonate in 100 ml. of ethanol was heated at reflux for 4.5 hours. The solution was evaporated and the residue was slurried with methylene chloride and filtered to remove 1.07 g. of water-soluble precipitate which was discarded. The filtrate was washed with 1*N* hydrochloric acid, dried and evaporated. The residue was recrystallized from ethanol to yield 1.08 g. of **11**, which was the salt of 5-hydroxy-3-methyl-1-(6-chloro-3-pyridazinyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (**12**) with 6-chloro-3-methyltriazolo[4,3-*b*]pyridazine (**10**), m.p. 181-182°. Another recrystallization (ethanol) gave 0.600 g. of **11**, m.p. 181-182°; ir (potassium bromide): 3200-2200 (broad stretching), 1720 (C=O), 1655, 1420, 1165, 1080, 1035 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.68 (d, J = 10 Hz, 1H, pyridazine H at 4-position of pyridazinylpyrazole), 8.39 (d, J = 10 Hz, 1H, pyridazine H at 8-position of triazolopyridazine), 8.02 (d, J = 10 Hz, 1H, pyridazine H at 5-position of pyridazinylpyrazole), 7.43 (d, J = 10 Hz, 1H, pyridazine H at 7-position of triazolopyridazine), 4.17 (q, J = 7.5 Hz, 2H, CH_2), 2.67 (s, 3H, triazole CH_3), 2.47 (s, 3H, pyrazole CH_3), 1.25 (t, J = 7.5 Hz, 3H, CH_2CH_3); ms: (70 eV, chemical ionization, methane) m/e 283 (M^++1), 311 (M^++29), and 323 (M^++41) for the pyridazinylpyrazole portion; and m/e 169 (M^++1), 197 (M^++29), and 209 (M^++41) for the triazolopyridazine portion.

Anal. Calcd. for $C_{17}H_{16}Cl_2N_8O_5$: C, 45.24; H, 3.57; N, 24.83. Found: C, 45.40; H, 3.74; N, 24.64.

The filtrate from the initial ethanol recrystallization of **11** was concentrated to give 0.460 g. of **10** as long, clear prisms. The concentrated filtrate was recrystallized from toluene-hexane to give an additional 1.65 g. of **10**. Total yield of **10** was 2.11 g., m.p. 106-107° [lit. (7) m.p. 103.5°]; ir (Nujol): 1510, 1365, 1325, 1150, 1080, 990, 810, 750 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.41 (d, J = 10 Hz, 1H, H at 8-position), 7.44 (d, J = 10 Hz, 1H, H at 7-position), 2.67 (s, 3H, CH_3); ms: (70 eV, chemical ionization, methane) m/e 169 (M^++1), 197 (M^++29), 209 (M^++41).

The 0.600 g. (1.33 mmoles) of **11** was dissolved in methylene chloride and *ca.* 20 ml. of 1*N* sodium hydroxide was added. The resulting insoluble white solid (sodium salt of **12**) was collected, washed with water and methylene chloride and then portioned between 1*N* hydrochloric acid and methylene chloride. The methylene chloride layer was dried (sodium sulfate) and concentrated to leave 0.295 g. (78%) of **12**; m.p. 193-195° (ethanol); ir (Nujol): 3250-2500 (OH), 1715 (C=O), 1650 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.71 (d, J = 10 Hz, 1H, pyridazine H at 4-position), 8.05 (d, J = 10 Hz, 1H, pyridazine H at 5-position), 4.18 (q, J = 7.5 Hz, 2H, CH_2), 2.48 (s, 3H, pyrazole CH_3), 1.25 (t, J = 7.5 Hz, 3H, CH_2CH_3); ms: (70 eV, electron impact) m/e 282 (molecular ion).

Anal. Calcd. for $C_{11}H_{11}ClN_4O_3$: C, 46.73; H, 3.92; N, 19.82. Found: C, 46.96; H, 4.08; N, 19.94.

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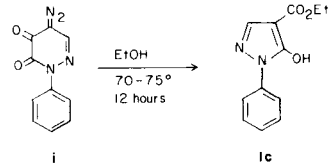

i Ic

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