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RADICALIC ETHOXYCARBONYLATION OF 3-IODO-PYRIDAZINES: AN EFFICIENT ACCESS TO TRI- AND TETRASUBSTITUTED PYRIDAZINES

Norbert Haider* and Johann Käferböck

Institute of Pharmaceutical Chemistry, University of Vienna
Althanstraße 14, A-1090 Vienna, Austria

Abstract – Introduction of ester groups into positions 4 and 5 of 3-iodo-pyridazines (**1**,**2**) by redox decomposition of the oxyhydroperoxide of ethyl pyruvate in a sulfuric acid/toluene two-phase system affords trifunctional pyridazine building blocks (**3**,**4a**) in a single step.

Iodoarenes and -hetarenes are known as useful synthons for C-C bond formation by palladium-catalyzed cross-coupling reactions.[1-8] In the pyridazine series, a number of alkynyl and aryl derivatives have been prepared in good yields from iodo precursors, using this methodology,[9-11] although in some cases also chloro-, bromo-, or trifluoromethanesulfonyloxypyridazines have been successfully employed as substrates for Pd^0-catalyzed introduction of carbon substituents.[12-14] The limited availability of iodopyridazines other than the 3-iodo and easily accessible 6-substituted 3-iodo derivatives, however, restricts the scope of this reaction type for the synthesis of polyfunctional 1,2-diazines. In particular, only very few iodo-substituted pyridazinecarboxylic acid derivatives have been described so far.[15-17] Here, we wish to report on a facile and convenient access to 3-iodo-4,5-pyridazinedicarboxylic acid diethyl ester and its 6-methyl congener, which were required in our laboratory as key intermediates for the construction of polycyclic condensed systems, by means of radicalic ethoxycarbonylation of the corresponding iodopyridazines.

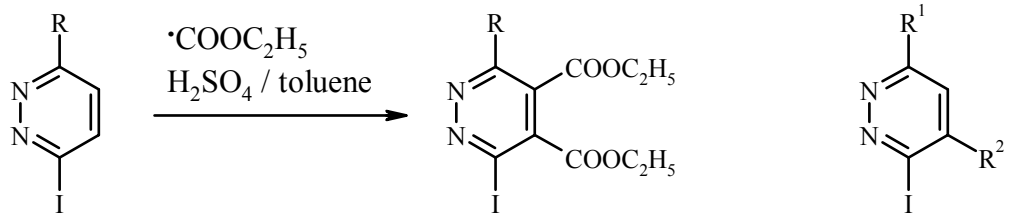
Since the pioneering work of Minisci,[18] nucleophilic carbon-centered radicals, including alkyl, acyl, carbamoyl and alkoxycarbonyl radicals, have found wide application for substitution reactions in π-

* *Dedicated with best wishes to Prof. Dr. F. Sauter on the occasion of his 70th birthday*

electron-deficient heteroaromatics.[19,20] For instance, the introduction of ester groups into the pyridazine nucleus by Fe^{2+}-induced redox decomposition of ethyl pyruvate oxyhydroperoxide in the presence of the protonated diazine has been investigated by Heinisch and Lötsch, who could achieve a significant selectivity enhancement by running the reaction in a sulfuric acid/dichloromethane two-phase system instead of the "standard" homogeneous solution.[21,22] Thus, diethyl pyridazine-4,5-dicarboxylate had been obtained in 65% yield from pyridazine, and the formation of previously observed polysubstituted side products was almost completely suppressed under these conditions.[21] So far, only one example of a halogen-containing pyridazine, namely 3-chloro-6-methylpyridazine has been subjected to radicalic alkoxycarbonylation. By this method, Dal Piaz had prepared diethyl 3-chloro-6-methylpyridazine-4,5-dicarboxylate in approx. 40% yield.[23] We now examined the possibility to introduce ester functionalities into 3-iodo-6-methylpyridazine[24] (**1**) and 3-iodopyridazine[16] (**2**). For the latter compound, we developed a new, convenient synthesis based on oxidative dehydrazination of 6-iodo-3-pyridazinylhydrazine which is easily available from the known 3,6-diiodopyridazine.[25,26]

Initial experiments showed that under two-phase conditions using dichloromethane as the organic layer, protonated compounds (**1**,**2**) indeed undergo radicalic ethoxycarbonylation in high conversion rates, as revealed by GC/MS and ^{1}H-NMR analyses of the crude reaction mixtures. Moreover, we found that the yield of the corresponding diester can be optimized by using toluene instead of dichloromethane as the organic solvent in this process. By this method, diethyl 3-iodo-6-methylpyridazine-4,5-dicarboxylate (**3**) was obtained from compound (**1**) in excellent yield (94%).

Scheme 1



1 R = CH_3
2 R = H

3 R = CH_3
4a R = H

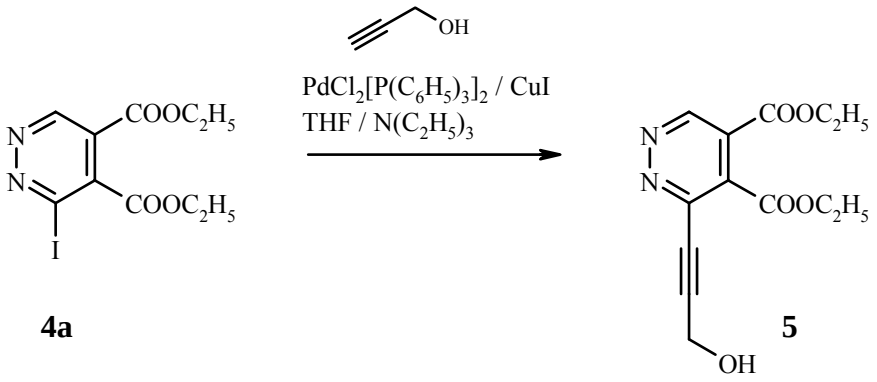
4b $R^1 = R^2 = COOC_2H_5$
4c $R^1 = COOC_2H_5$, R^2 = H
4d R^1 = H, $R^2 = COOC_2H_5$

Under the same conditions, employment of the monosubstituted iodopyridazine (**2**) afforded diethyl 3-iodopyridazine-4,5-dicarboxylate (**4a**) in good yield. In this case, however, formation of three side

products (see Scheme 1) was observed and they could be isolated by column chromatography. According to ^{1}H-NMR, the crude reaction mixture contains the main product (**4a**), its isomer (**4b**), and the two monoesters (**4c**, **4d**) in a ratio of 100 : 11 : 7 : 13. Structure assignments are mainly based on ^{1}H-NMR data (including NOE experiments) as well as on comparison of the ^{13}C-NMR data with those reported for related pyridazine derivatives.[27] When 3-iodo-6-phenylpyridazine was employed as an ethoxycarbonylation substrate, it was recovered unchanged and only a trace of a monosubstitution product could be detected by GC/MS. This lack of reactivity is in agreement with previous observations reported for 3-chloro-6-phenylpyridazine in this reaction type.[23]

The described method is experimentally simple, uses easily available starting materials and reagents and thus provides a convenient access to the new iodo-substituted pyridazinedicarboxylic acid esters (**3**) and (**4a**). These compounds should be useful synthons, especially in Pd^{0}-catalyzed cross-coupling reactions, as exemplified by the smooth conversion of **4a** into diethyl 3-(3-hydroxy-1-propynyl)pyridazine-4,5-dicarboxylate (**5**) under Sonogashira conditions.

Scheme 2



4a **5**

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded for KBr pellets on an Perkin-Elmer 1605 FT-IR instrument; ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Varian Unity*plus* 300 spectrometer (TMS as internal reference, δ values in ppm). MS spectra were obtained with a Hewlett-Packard 5890A/5970B GC/MS spectrometer.

HRMS spectra were taken on a Finnigan MAT 8230 instrument at the Institute of Organic Chemistry, University of Vienna. Column chromatography was done on Merck Kieselgel 60, 0.063-0.200 mm. Light petroleum refers to the fraction of bp 50-70°C. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

6-Iodo-3-pyridazinylhydrazine

A mixture of 3,6-diiodopyridazine (33.2 g, 0.1 mol),[25,26] hydrazine hydrate (100%, 50.0 g, 1 mol), and 200 mL ethanol was refluxed for 5 h. After cooling, the volatile components were removed under reduced pressure. The residue was triturated with water, filtered off, and dried to afford 6-iodo-3-pyridazinyl-hydrazine (21.5 g; 91%) as colorless crystals, mp 138-140°C (ethanol). *Anal.* Calcd for $C_4H_5N_4I$: C, 20.36; H, 2.14; N, 23.74. Found: C, 20.57; H, 2.08; N, 23.67. MS: *m/z* (rel. int.) 236 (M^+, 100%), 165 (18), 127 (42), 79 (26), 64 (58), 56 (21), 54 (66), 52 (49). IR (cm^{-1}): 3273, 3025, 1579, 1401, 1494, 1179, 1052, 844, 637. ^{1}H-NMR (DMSO-d_6) δ: 8.13 ppm (s, 1H, NH), 7.59 (d, $J_{4\text{-}5}$ = 9.3 Hz, 1H, H-5), 6.80 (d, $J_{4\text{-}5}$ = 9.3 Hz, 1H, H-4), 4.40 (s, 2H, NH_2).

3-Iodopyridazine[16,28]

To a vigorously stirred suspension of yellow mercuric oxide (38.9 g, 0.18 mol) in water (450 mL) was added finely ground 6-iodo-3-pyridazinylhydrazine (21.2 g, 0.09 mol) in small portions over a period of 1.5 h. Stirring was continued for 2 h, then the mixture was extracted several times with ethyl acetate. After drying with Na_2SO_4, the combined extracts were filtered and evaporated to afford 3-iodopyridazine (12.6 g, 68%) as a light brown solid, mp 121-123°C (ethyl acetate) (lit.,[16] 125°C, lit.,[28] 152°C).

Diethyl 3-Iodo-6-methylpyridazine-4,5-dicarboxylate (**3**)

A 30% solution of hydrogen peroxide (3.4 g, 0.03 mol) was added dropwise at -10° - 0°C to ethyl pyruvate (5.2 g, 0.045 mol) with stirring. The viscous liquid was kept at the same temperature for 15 min, then it was added dropwise to a vigorously stirred mixture of 3-iodo-6-methylpyridazine[24] (2.2 g, 0.01 mol), water (4 mL), concentrated sulfuric acid (3.0 g, 0.03 mol), $FeSO_4 \cdot 7\ H_2O$ (8.3 g, 0.03 mol), and toluene (30 mL) at -5°C - 0°C. Stirring was continued for another 15 min, then the mixture was poured into ice-water and it was extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. Excess ethyl pyruvate was removed by Kugelrohr distillation at 10^{-2} mbar/30°C. The residue was purified by column chromatography (ethyl acetate/light petroleum, 1:2) to afford **3** (3.42 g, 94%) as a yellow oil which slowly solidified, mp 57-63°C. *Anal.* Calcd for

$C_{11}H_{13}N_2O_4I$: C, 36.28; H, 3.60; N, 7.69. Found: C, 36.56; H, 3.56; N, 7.53. MS: *m/z* (rel. int.) 364 (M^+, 100%), 318 (24), 291 (31), 262 (10), 234 (7), 219 (20), 191 (10), 163 (10), 151 (18), 137 (23), 127 (9), 109 (14), 91 (37), 78 (15), 63 (37), 52 (8). IR (cm^{-1}): 2975, 2930, 1735, 1724, 1370, 1314, 1279, 1233, 1155, 1010, 856. ^{1}H-NMR ($CDCl_3$) δ: 4.50-4.35 ppm (m, 4H, $C\underline{H}_2CH_3$), 2.81 (s, 3H, CH_3), 1.48-1.33 (m, 6H, $CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.5 ppm (C=O), 163.4 (C=O), 156.7 (C-6), 136.4 (C-5), 127.6 (C-4), 119.9 (C-3), 63.2 ($\underline{C}H_2CH_3$), 63.1 ($\underline{C}H_2CH_3$), 20.9 (CH_3), 13.87 ($CH_2\underline{C}H_3$), 13.85 ($CH_2\underline{C}H_3$).

Radicalic Ethoxycarbonylation of 3-Iodopyridazine (**3**)

A 30% solution of hydrogen peroxide (3.4 g, 0.03 mol) was added dropwise at -10° - 0°C to ethyl pyruvate (5.2 g, 0.045 mol) with stirring. The viscous liquid was kept at the same temperature for 15 min, then it was added dropwise to a vigorously stirred mixture of 3-iodopyridazine (**3**) (2.06 g, 0.01 mol), water (4 mL), concentrated sulfuric acid (3.0 g, 0.03 mol), $FeSO_4 \cdot 7\ H_2O$ (8.3 g, 0.03 mol), and toluene (30 mL) at -5°C - 0°C. Stirring was continued for another 15 min, then the mixture was poured into ice-water and it was extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated (bath temperature max. 30°C). Excess ethyl pyruvate was removed by Kugelrohr distillation at 10^{-2} mbar/30°C. The oily residue (3.4 g) thus obtained consisted of a mixture of compounds (**4a**, **4b**, **4c**, and **4d**) in a ratio of 100 : 11 : 7 : 13 (^{1}H-NMR) and it was subjected to column chromatography (ethyl acetate/light petroleum, 1:2). The *first fraction* afforded 2.48 g (71%) of crude diethyl 3-iodopyridazine-4,5-dicarboxylate (**4a**) as a yellow oil which slowly turned into a wax-like solid. This material still contained small amounts of **4b** (see below) and it was purified by repeated column chromatography (toluene/ethyl acetate, 19:1) to give a colorless oil which slowly solidified, mp 69-72°C. *Anal.* Calcd for $C_{10}H_{11}N_2O_4I$: C, 34.31; H, 3.17; N, 8.00. Found: C, 34.07; H, 3.06; N 7.85. MS: *m/z* (rel. int.) 350 (M^+, 100%), 305 (12), 277 (45), 205 (27), 176 (48), 149 (19), 137 (24), 127 (29), 123 (16), 111 (13), 95 (22), 77 (35), 67 (14), 50 (25). IR (cm^{-1}): 2978, 1744, 1731, 1542, 1375, 1325, 1281, 1223, 1184, 1019, 736. ^{1}H-NMR ($CDCl_3$) δ: 9.55 ppm (s, 1H, H-6), 4.50 (q, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 4.43 (q, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 1.43 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 1.39 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.5 (C=O), 161.5 (C=O), 148.6 (C-6), 138.8 (C-4), 124.3 (C-5 or C-3), 123.4 (C-3 or C-5), 63.34 ($\underline{C}H_2CH_3$), 63.30 ($\underline{C}H_2CH_3$), 13.9 ($CH_2\underline{C}H_3$), 13.8 ($CH_2\underline{C}H_3$). The *second fraction* contained a mixture of **4a** and **4b**. Repeated column chromatography (toluene/ethyl acetate, 19:1) with careful fraction cutting gave a sample of pure diethyl 6-iodopyridazine-3,5-dicarboxylate (**4b**) as a yellow oil. HRMS Calcd for $C_{10}H_{11}N_2O_4I$: 349.9764. Found: 349.9773. MS: *m/z* (rel. int.) 350 (M^+, 3%), 306 (28), 278 (33), 249 (4), 176 (7), 151 (61), 127 (12), 123 (100), 105 (13), 77 (20), 53 (6). IR (cm^{-1}): 2983, 1737, 1370, 1252, 1084, 1014. ^{1}H-NMR ($CDCl_3$) δ: 8.24 ppm (s, 1H, H-4), 4.55 (q, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$),

4.48 (q, J = 7.2 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.52-1.40 (m, 6H, CH$_2$C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.5 ppm (C=O), 163.2 (C=O), 151.2 (C-3), 136.3 (C-5), 126.8 (C-4), 126.3 (C-6), 63.4 ($\underline{C}H_2CH_3$), 63.1 ($\underline{C}H_2CH_3$), 14.2 ($CH_2\underline{C}H_3$), 14.0 ($CH_2\underline{C}H_3$). The *third fraction* afforded ethyl 6-iodopyridazine-3-carboxylate (**4c**) (0.104 g, 4%) as colorless crystals, mp 124-127°C (ether). *Anal.* Calcd for $C_7H_7N_2O_2I$: C, 30.24; H, 2.54; N, 10.07. Found: C, 30.48; H.2.52; N 10.03. MS: *m/z* (rel. int.) 278 (M^+, 9%), 234 (100), 206 (87), 152 (19), 127 (45), 79 (81), 52 (40), 45 (35). IR (cm^{-1}): 3103, 3043, 2976, 1736, 1547, 1365, 1295, 1146, 1104, 1028, 787, 732. ^{1}H-NMR ($CDCl_3$) δ: 8.04 ppm (d, $J_{4\text{-}5}$ = 8.7 Hz, 1H, H-4), 7.82 (d, $J_{4\text{-}5}$ = 8.7 Hz, 1H, H-5), 4.54 (q, J = 7.2 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.50 (t, J = 7.2 Hz, 3H, CH$_2$C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.7 ppm (C=O), 150.9 (C-3), 137.9 (C-4), 128.4 (C-6), 128.0 (C-5), 62.8 ($\underline{C}H_2CH_3$), 14.1 ($CH_2\underline{C}H_3$). The *fourth fraction* gave ethyl 3-iodopyridazine-4-carboxylate (**4d**) (0.184 g, 7%) as a yellow wax-like solid, mp <30°C, which slowly turned dark at rt. HRMS Calcd for $C_7H_7N_2O_2I$: 277.9552. Found: 277.9541. MS: *m/z* (rel. int.) 278 (M^+, 75%), 250 (10), 233 (8), 177 (20), 127 (35), 95 (8), 77 (18), 67 (22), 50 (100), 43 (20). IR (cm^{-1}): 3045, 2981, 1728, 1390, 1318, 1277, 1179, 1066, 1023, 780, 729. ^{1}H-NMR ($CDCl_3$) δ: 9.25 ppm (d, $J_{5\text{-}6}$ = 5.1 Hz, 1H, H-6; shows positive NOE on irradiation at 7.65 ppm), 7.65 (d, $J_{5\text{-}6}$ = 5.1 Hz, 1H, H-5; shows positive NOE on irradiation at 9.25 ppm), 4.47 (q, J = 7.2 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.44 (t, J = 7.2 Hz, 3H, CH$_2$C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.9 ppm (C=O), 150.4 (C-6), 135.6 (C-4), 125.9 (C-5), 123.2 (C-3), 63.1 ($\underline{C}H_2CH_3$), 14.0 ($CH_2\underline{C}H_3$).

Diethyl 3-(3-Hydroxy-1-propynyl)pyridazine-4,5-dicarboxylate (**5**)

To a solution of **4a** (0.91 g, 2.6 mmol) and propargyl alcohol (0.18 g, 3.2 mmol) in THF (6 mL) were added triethylamine (1 mL, 7.2 mmol), CuI (0.015 g, 3 mol%), and $PdCl_2(PPh_3)_2$ (0.055 g, 3 mol%). The suspension was stirred at rt for 7 h under an argon atmosphere. Insoluble material was filtered off and washed thoroughly with THF. The filtrate and washing were evaporated under reduced pressure and the residual brown oil was subjected to column chromatography (ethyl acetate/light petroleum, 3:2) to afford compound (**5**) (0.52 g, 72%) as an almost colorless oil. HRMS Calcd for $C_{13}H_{14}N_2O_5$: 278.0903. Found: 278.0907. MS: *m/z* (rel. int.) 278 (M^+, 100%), 249 (17), 233 (25), 176 (35), 165 (34), 148 (38), 121 (41), 87 (83), 77 (53), 76 (59), 75 (62), 51 (43), 50 (42). IR (cm^{-1}): 3289, 2981, 2940, 2902, 2233, 1738, 1725, 1371, 1342, 1303, 1214, 1075, 1041, 1027, 755, 746, 589. ^{1}H-NMR ($CDCl_3$) δ: 9.56 ppm (s, 1H, H-6), 4.57 (d, J = 3.9 Hz, 2H, C$\underline{H}_2$OH), 4.49 (q, J = 7.2 Hz, 2H, C$\underline{H}_2$CH$_3$), 4.44 (q, J = 7.2 Hz, 2H, C$\underline{H}_2$CH$_3$), 2.81 (br t, unresolved, 1H, OH), 1.42 (t, J = 7.2 Hz, 3H, CH$_2$C$\underline{H}_3$), 1.40 (t, J = 7.2 Hz, 3H, CH$_2$C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.0 ppm (C=O), 162.2 (C=O), 147.5 (C-6), 144.5 (C-3), 134.0 (C-4), 123.8 (C-5), 97.1 (alkyne-C), 79.0 (alkyne-C), 63.2 ($\underline{C}H_2CH_3$), 63.1 ($\underline{C}H_2CH_3$), 51.2 ($\underline{C}H_2OH$), 14.0 ($CH_2\underline{C}H_3$), 13.9 ($CH_2\underline{C}H_3$).

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