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PYRIDAZINES - 61.[1] UNEXPECTED REACTION BEHAVIOUR OF PYRIDAZINECARBONITRILE DERIVATIVES TOWARDS PHENYLMAGNESIUM CHLORIDE

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Abstract Reactions of 4-cyano-3(2*H*)-pyridazinone (**1**) and tetrazolo[1,5-*b*]pyridazine-8-carbonitrile (**4**) with phenylmagnesium chloride were found to be governed by formal replacement of the nitrile function to afford the phenyl-substituted pyridazine derivatives **3** and **5** rather than the expected aryl heteroaryl ketones

The reaction of N-heteroaromatic carbonitriles with Grignard reagents is a well-established approach to alkyl- and aryl-heteroaryl ketones, which has been successfully applied also in the pyridazine series Thus, phenyl 3-pyridazinyl ketone[2] as well as several alkyl 3-pyridazinyl ketones[3,4] have been prepared from 3-pyridazinecarbonitrile and the appropriate aryl or alkylmagnesium halides Also with some 4-cyano-3(2*H*)-pyridazinones bearing additional substituents at positions 2, 5, and 6, such conversions into the corresponding ketones have been reported [5]

In the course of ongoing studies on the preparation and utilisation of aryl 4-pyridazinyl ketones bearing an additional functional group (OH, NH_2) at the pyridazine ring,[6-8] we now observed an interesting reaction behaviour of the conveniently available nitriles 4-cyano-3(2*H*)-pyridazinone[9] (**1**) and tetrazolo[1,5-*b*]pyridazine-8-carbonitrile[10] (**4**) towards phenylmagnesium chloride. Surprisingly, when **1** was treated with this Grignard reagent in tetrahydrofuran solution at 0°C, only minor amounts (20%) of the expected ketone **2** were

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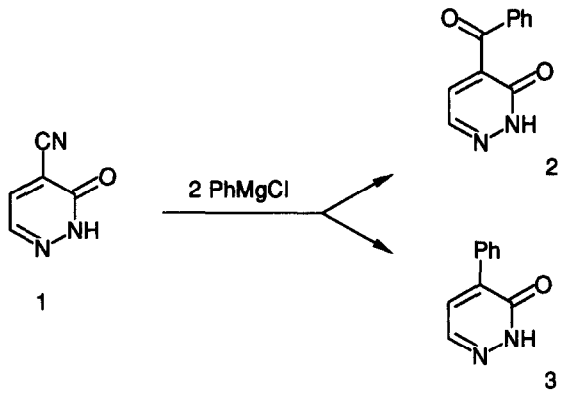
formed, whereas the molecular formula $C_{10}H_8N_2O$ of the main product (70%) suggested the structure of a phenylpyridazinone A comparison of the physicochemical data of this product with the data reported for the three isomeric phenyl-3(2*H*)-pyridazinones[11-13] finally revealed structure **3** [14]

Scheme 1

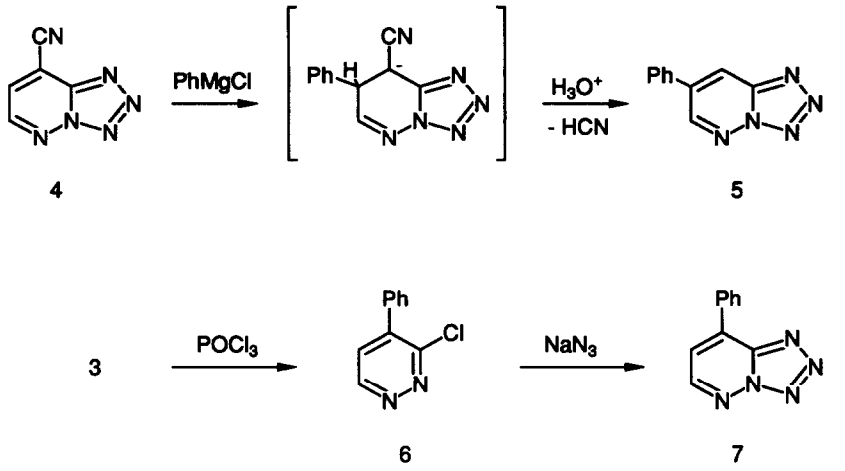


Thus, **1** is preferentially attacked at the pyridazine C-4 ring carbon atom (rather than at the nitrile function) Subsequent expulsion of the CN moiety then affords compound **3**

Scheme 2

In view of the previously reported smooth degradation of tetrazolo[1,5-*b*]pyridazines to 3-amino-pyridazines,[10,15] also the nitrile **4** was considered an attractive starting material for *ortho*-difunctionalised pyridazines like 3-amino-4-pyridazinyl aryl ketones However, when compound **4** was treated with phenyl-magnesium chloride under the conditions described above, again (formal) replacement of the cyano function by a phenyl group took place, as indicated by elemental analysis, here, only one product (compound **5**) could be isolated (yield 90%) In contrast to the findings with the oxonitrile **1**, in this case the ring position attacked by the Grignard reagent was found not to be the carbon atom bearing the nitrile group [16] This could be proven by an unequivocal synthesis of 8-phenyltetrazolo[1,5-*b*]pyridazine (**7**) from compound **3** *via* the chloro-pyridazine derivative **6** and comparison with the reaction product **5** mentioned above

Scheme 3



A coupling constant of 2 2 Hz observed for the two pyridazine protons (suggesting *meta* position) in the ^{1}H-NMR spectrum of compound **5** led to the assignment of the 7-phenyltetrazolo[1,5-*b*]pyridazine structure displayed in Scheme 3 This assumption finally could be confirmed by NOE difference spectroscopy a positive NOE was observed for the phenyl *ortho* protons upon irradiation of H-6 (δ 9.46) as well as of H-8 (δ 9 10) (compare Fig 1)

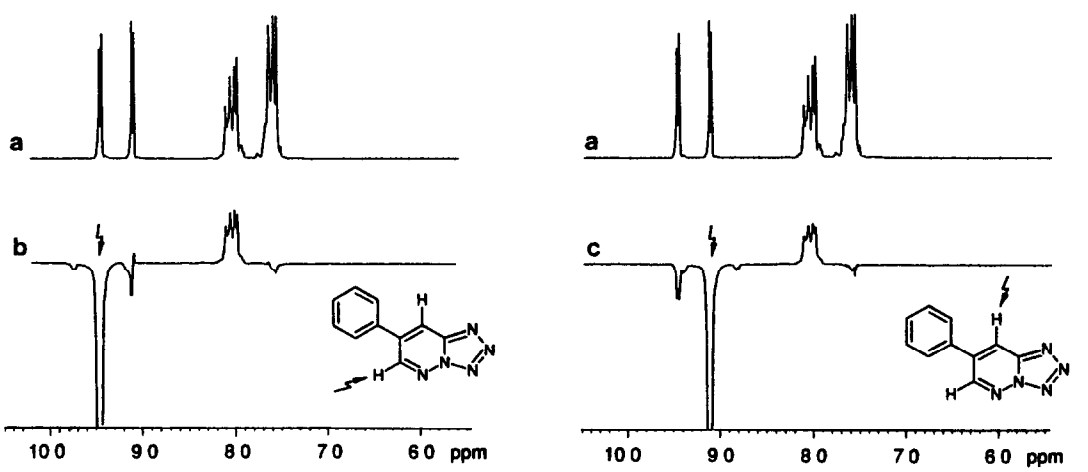


Figure 1 a) ^{1}H-NMR spectrum of compound **5** b) NOE difference spectrum of **5** resulting from irradiation of H-6
c) NOE difference spectrum of **5** resulting from irradiation of H-8

The surprising findings with compound **4** prompted us to reexamine the reaction mixture obtained from the oxonitrile **1** and, indeed, also in this case we were able to isolate - albeit in very low yield (1%) - a product formed by attack of the Grignard reagent *ortho* to the nitrile function [i.e. 5-phenyl-3(2*H*)-pyridazinone[11,12]]

Whereas there are some reports in the literature on the nucleophilic displacement of a CN group in nitriles derived from condensed pyrimidines or from 1,2,4-triazines in reactions with Grignard reagents,[17] the reaction behaviour now observed with the nitriles **1** and **4** obviously is unprecedented in the pyridazine series. The surprising regioselectivity[18] leading to the 7-phenyl compound **5** from the 8-cyanotetrazolopyridazine **4**, to our knowledge, is without any precedent.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Infrared spectra were taken on a Jasco IRA-1 spectrophotometer. ^{1}H-NMR spectra were recorded on either a Varian EM 390 (90 MHz), a Bruker AC 80 (80 MHz), or a Bruker AM 400 (400 MHz) spectrometer with TMS as internal reference. Mass spectra were obtained with a Hewlett-Packard 5890A/5970B-GC/MSD spectrometer. Column chromatography was carried out on Merck Kieselgel 60, 0.063-0.200 mm (70-230 mesh ASTM). Microanalyses were performed by Mag J Theiner, Institute of Physical Chemistry, University of Vienna

Reaction of 4-Cyano-3(2*H*)-pyridazinone (**1**) with Phenylmagnesium Chloride

To a solution of the nitrile **1**[9] (968 mg, 8 mmol) in dry tetrahydrofuran (40 ml) was added phenylmagnesium chloride (10 ml of a 2 *M* solution in tetrahydrofuran, 20 mmol) under an argon atmosphere at 0°C, then the solution was stirred for 20 h at room temperature After addition of 2 *N* hydrochloric acid (20 ml), the mixture was stirred for 10 min; then it was concentrated *in vacuo* to a volume of about 20 ml The resulting suspension was extracted exhaustively with dichloromethane. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was subjected to column chromatography (eluting with ethyl acetate-light petroleum, 1 1) Evaporation of the first fraction, followed by further chromatographic separation (light petroleum-methanol-diethyl ether, 75·15:10, as eluant) and subsequent recrystallisation from ethanol afforded 5-phenyl-3(2*H*)-pyridazinone[12] (14 mg, 1%) and 4-phenyl-3(2*H*)-pyridazinone[11] (**3**) (965 mg, 70%), identified by comparison (IR) with authentic material ^{1}H-NMR data for compound **3** (DMSO-d_6) δ 13.50 (br s, 1 H, NH), 8.05 (d, J = 3 9 Hz, 1 H, pyridazine H-6), 7 85-7 80 (m, 2 H, phenyl H-2, H-6), 7 73-7 68 (m, 1 H, phenyl H-4), 7 59 (d, J = 3 9 Hz, 1 H, pyridazine H-5), 7 57-7 53 (m, 2 H, phenyl H-3, H-5)

Evaporation of the second fraction, followed by recrystallisation from ethanol, gave (2,3-dihydro-3-oxo-4-pyridazinyl)phenyl ketone (**2**) (320 mg; 20%) as colourless crystals, mp 215-217°C.
^{1}H-NMR (DMSO-d_6) δ 13 25 (br s, 1 H, NH), 7.95 (d, J = 4 1 Hz, 1 H, pyridazine H-6), 7.90-7.83 (m, 2 H, phenyl H-2, H-6), 7 59 (d, J = 4 1 Hz, pyridazine H-5), 7 50-7 42 (m, 3 H, phenyl H-3, H-4, H-5).
Anal. Calcd for $C_{11}H_8N_2O_2$ C, 66 00; H, 4 03; N, 13 99 Found C, 65 76; H, 4.08, N, 14.14

7-Phenyltetrazolo[1,5-*b*]pyridazine (**5**)

To a solution of tetrazolo[1,5-*b*]pyridazine-8-carbonitrile[10] (**4**) (292 mg, 2 mmol) in dry tetrahydrofuran (10 ml) was added phenylmagnesium chloride (1 5 ml of a 2 *M* solution in tetrahydrofuran, 3 mmol) under an argon atmosphere at 0°C, then the solution was stirred for 4 h at room temperature After addition of 2 *N* hydrochloric acid (2 ml), the mixture was stirred for 30 min, then it was concentrated *in vacuo* to a volume of about 2 ml The resulting suspension was diluted with water and extracted exhaustively with dichloromethane The extract was washed with water, dried (Na_2SO_4), and evaporated Recrystallisation of the residue from ethanol afforded colourless crystals (355 mg, 90%), mp 193-194°C
^{1}H-NMR (DMSO-d_6) δ 9 46 (d, J = 2 2 Hz, 1 H, H-6), 9 10 (d, J = 2 2 Hz, 1 H, H-8), 8.10-7 95 (m, 2 H, phenyl H-2, H-6, shows NOE on irradiation at 9 46 ppm as well as on irradiation at 9.10 ppm), 7.65-7 50 (m, 3 H, phenyl H-3, H-4, H-5)
Anal Calcd for $C_{10}H_7N_5$ C, 60 91, H, 3 58, N, 35.51 Found C, 60 64, H, 3 67, N, 35 85

3-Chloro-4-phenylpyridazine (**6**)[20]

A solution of 4-phenyl-3(2*H*)-pyridazinone (**3**) (344 mg, 2 mmol) in phosphoryl chloride (6 ml) and pyridine (3 drops) was stirred at 110°C for 2 h. After cooling, the solution was poured onto ice and extracted with dichloromethane The extract was washed with saturated aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4) and evaporated Recrystallisation from cyclohexane gave colourless crystals (360 mg, 94%), mp 97-109°C
^{1}H-NMR ($CDCl_3$) δ 8 20 (d, J = 5 5 Hz, 1 H, pyridazine H-6), 7.65-7 30 (m, 6 H, C_6H_5, pyridazine H-5)
Anal Calcd for $C_{10}H_7ClN_2$ C, 63 01, H, 3 70, N, 14 69. Found C, 63 07; H, 3 80, N, 14.63

8-Phenyltetrazolo[1,5-*b*]pyridazine (**7**)

To a solution of 3-chloro-4-phenylpyridazine (**6**) (572 mg, 3 mmol) in dimethylformamide (10 ml) was added sodium azide (260 mg, 4 mmol), and the mixture was stirred for 20 h at 120°C After evaporation of the solvent *in vacuo*, the residue was taken up in water and extracted with dichloromethane The organic layer was dried (Na_2SO_4) and evaporated Recrystallisation of the residue from ethyl acetate afforded colourless needles (402 mg, 68 %), mp 199°C
^{1}H-NMR ($CDCl_3$) δ 9 12 (d, J = 4 9 Hz, 1 H, H-6), 8 60-8 35 (m, 2 H, phenyl H-2, H-6), 8 24 (d, J = 4 9 Hz, 1 H, H-7), 7 85-7 60 (m, 3 H, phenyl H-3, H-4, H-5)
Anal Calcd for $C_{10}H_7N_5$ C, 60 91, H, 3 58, N, 35 51 Found C, 60 99, H, 3 65; N, 35 78

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