CONVENIENT PREPARATION OF 3-METHOXYCARBONYLPYRIDAZINES BY PALLADIUM CATALYZED ALKOXYCARBONYLATION OF PYRIDAZINETRIFLATES#

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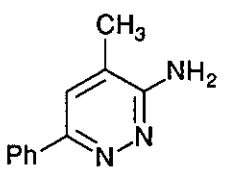
Abstract - The methoxycarbonylation of several pyridazine-trifluoromethanesulphonates with CO and MeOH is catalyzed by $Pd(OAc)_2$ and 1,1'-bis(diphenylphosphino)ferrocene. This method constitutes a mild and efficient homologation of pyridazinones.

For medicinal chemistry purposes we have largely used the pyridazine nucleus as core to design potent biological active compounds : specially the 3-amino-4-methyl-6-phenylpyridazine (**1**) proved to be of exceptional value.[1-3] From a chemical point of view we proposed recently two mild alkylation procedures of the pyridazine nucleus : (i) side chain elongation at C4 using the ortho-directed metalation of 3-heterosubstituted pyridazines,[4] (ii) alkylation at C3 starting from pyridazine triflates *via* a Pd° cross coupling reaction, providing an easy access to 3-alkynylpyridazines (**2**).[5] For another medicinal chemistry project, we needed to prepare the pyridazinecarboxylate (**5e**).[6]



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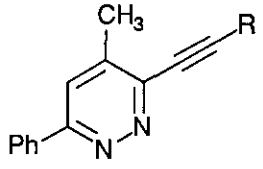
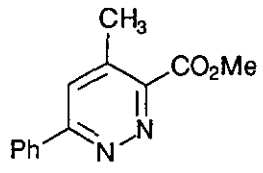


2 (R = CH_2OH, CH_2NHBoc)



5e

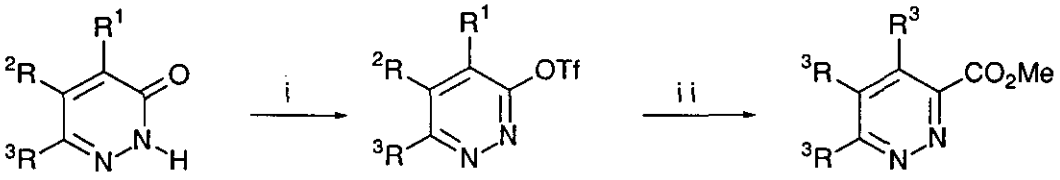
Scheme 1

A literature survey revealed that the preparation of this class of compounds needed at first a tedious ring elaboration, at second an oxidative cleavage of aliphatic side chains, or a vigorous hydrolysis of nitriles or amides.[6] Therefore we decided to investigate the alkoxy-

#This paper is dedicated to Professor Miha Tisler from the University of Ljubljana (Slovenia) on the occasion of its 70th birthday.

carbonylation of triflates deriving from pyridazines as an alternative route for the preparation of compound (**5e**) and analogs. Transition metal catalyzed carbonylation of aryl or heteroaryl triflates in presence of alcohols or even amines is now a convenient and reliable method for the direct introduction of a carbonyl group into a molecule.[7] But to the best of our knowledge no example related to pyridazinones is reported. In this paper, we present our results concerning the methoxycarbonylation of diversely substituted pyridazines under cross coupling conditions *via* their triflates obtained from the corresponding pyridazinones.

The pyridazinetriflates (**4a-f**) were directly prepared by reaction of triflic anhydride in pyridine at room temperature on the easily accessible pyridazinones (**3a-f**).[1,2,5] The triflates were purified by column chromatography generally and obtained as solids in good to excellent yields which can be stored at 0°C without notable decomposition.



3a $R^1 = R^2 = H$, $R^3 = Me$	**4a**	(90%)	**5a**	(62%)
3b $R^1 = R^2 = H$, $R^3 = Ph$	**4b**	(82%)	**5b**	(86%)
3c $R^1 = H$, $R^2 = Me$, $R^3 = 2,4\text{-diCl-Ph}$	**4c**	(77%)	**5c**	(49%)
3d $R^1 = H$, $R^2 = Me$, $R^3 = Ph$	**4d**	(72%)	**5d**	(73%)
3e $R^1 = Me$, $R^2 = H$, $R^3 = Ph$	**4e**	(72%)	**5e**	(68%)
3f $R^1 = Me$, $R^2 = H$, $R^3 = 4\text{-F-Ph}$	**4f**	(68%)	**5f**	(72%)

Reagents: i) Tf_2O, pyridine, 20°C; ii) CO (balloon), $Pd(OAc)_2$, dppf, TEA, MeOH, DMF, 50°C.

Scheme 2

To perform the carbonylation of the triflates (**4a-f**), we tried at first the experimental conditions reported originally by Cacchi.[9] Accordingly for the oxidative insertion of palladium we used palladium acetate in presence of triphenylphosphine in a mixture of DMF and MeOH under a CO atmosphere (CO balloon), but no significant reaction was observed after 1 day at 50°C. Switching to 1,1'-bis(diphenylphosphino)ferrocene (DPPF) as a ligand for Pd as recommended,[9,10] the reaction proceeded at room temperature but is accelerated significantly at 50°C to yield the pyridazinecarboxylates (**5a-f**). The reaction was complete after 6 h to 12 h. In all cases a clean reaction was observed and the

corresponding carboxylates were obtained in pure form, as solids. After purification by column chromatography, all compounds were fully characterized. As depicted on Scheme 2, we were able to prepare not only our target compound (**5e**), but additionally several other 3-methoxycarbonylpyridazines were prepared with the same experimental procedure. The palladium insertion in the pyridazinetriflates appears to be insensitive to stereoelectronic factors. In our hands the only limitation of this carbonylation is the stability of the triflates under the reaction conditions.

This mild and efficient methoxycarbonylation of pyridazines provides an entry to pyridazinecarboxylates hitherto difficult to prepare.

EXPERIMENTAL

^{1}H-Nmr spectra were performed on a Bruker SY 200 (200 MHz) spectrometer and recorded in $CDCl_3$ solutions. The residual $CHCl_3$ present in $CDCl_3$ was used as internal standard at 7.27 ppm. ^{13}C Nmr (50 MHz) spectra were recorded on the same instrument with $CDCl_3$ (δ=77 ppm) as reference. Tlc visualization was achieved by a uv lamp or spraying with 2% ethanolic phosphomolybdic acid and charring. Melting points were measured in open capillary tubes using a Gallenkampf apparatus, and are uncorrected. Purifications and separations by column chromatography were performed on silica gel, using the flash chromatography procedure. DMF was used after drying with molecular sieves. MeOH was taken directly from a fresh bottle.

3-Trifluoromethylsulfonylpyridazines (3a-f) : General Procedures :

In a 50 ml two-necked, round bottomed flask were introduced at 0°C under argon, the pyridazinone (17.4 mmol) and distilled pyridine (20 ml). Triflic anhydride (4.4 ml, 26.1 mmol) was added dropwise *via* a syringe. The reaction was allowed to reach room temperature over 6 h. Water (30 ml) was added and the mixture was extracted three times with CH_2Cl_2 (40 ml). The combined organic layers were washed with brine (30 ml) and dried over anhydrous Na_2SO_4. Filtration on Celite and evaporation *in vacuo* yielded a yellow solid which was purified by flash chromatography, eluting with a mixture of Et_2O / CH_2Cl_2 / hexane, 10 : 20 : 70. The physical data of triflates (**4a**), (**4b**) and (**4e**) are reported.[5]

6-(2',4'-Dichlorophenyl)-3-trifluoromethylsulfonyl-5-methylpyridazine (4c)

Yield : 77%; mp 112°C. ^{1}H-Nmr ($CDCl_3$) δ 2.32 (3H, s, CH_3), 7.33-7.58 (4H, m, arom.). ^{13}C-Nmr ($CDCl_3$) δ 18.9 (CH_3), 120 (CF_3, q, J = 310 Hz), 127.8 (CH), 129.7 (CH), 131.6 (CH), 133.2 (C), 133.7 (C), 136.5 (C), 143.7 (C), 159.6 (C), 161.7 (C). Anal. Calcd for $C_{12}H_7N_2O_3Cl_2F_3S$: C, 37.29; H, 1.82; N: 7.24. Found C: 37.45; H: 1.91; N: 7.39. Ms m/z = 386 (M^+, 2 x ^{35}Cl), 388 (M^+, ^{35}Cl and ^{37}Cl), 390 (M^+, 2 x ^{37}Cl).

3-Trifluoromethylsulfonyl-5-methyl-6-phenylpyridazine (4d)
Yield : 72%; mp 81°C. ^{1}H-Nmr ($CDCl_3$) δ 2.48 (3 H, s, CH_3), 7.39 (1 H, s, CH), 7.51-7.60 (m, 5 H, arom.). ^{13}C-Nmr ($CDCl_3$) δ 20.2 (CH_3), 118.6 (q, CF_3, J = 320 Hz), 121.2 (CH), 128.6 (CH), 129.1 (CH), 129.6 (CH), 135.2 (C), 142.0 (C), 158.9 (C), 163.6 5C). Ir (film) ν (cm^{-1}) : 3080 (w), 2359 (w); 2359 (w), 1569 (w), 1417 (s), 1214 (s), 1137 (s), 975 (m), 855 (m). Anal. Calcd for $C_{12}H_9N_2O_3F_3S$: C, 45.28; H, 2.85; N, 8.80; Found C, 45.41; H, 2.81; N, 8.72. Ms m/z = 185 (M^+).

3-Trifluoromethylsulfonyl-6-(4'-fluorophenyl)-4-methylpyridazine (4f)
Yield : 68%; mp 112°C. ^{1}H-Nmr ($CDCl_3$) δ 2.47 (3 H, s, CH_3), 7.18 (2 H, dd, J_{HH} = 8.6 Hz and J_{HF} = 8.6 Hz), 7.84 (s, 1 H, CH), 8.02 (dd, 2 H, J_{HH} = 8.6 Hz and J_{HF} = 5.3 Hz, arom.). ^{13}C-Nmr ($CHCl_3$) δ 15.6 (CH_3), 116.2 (d, J = 21.5 Hz), 129.2 (d, J = 8.3 Hz), 130.3 (C), 159.5 (C), 163.5 (d, $^1J_{CF}$ = 251 Hz). Ir (film) ν (cm^{-1}) : 3080 (w), 2362 (w), 1800 (w), 1514 (w), 1422 (m), 1407 (s), 1214 (s), 1132 (m), 929 (w), 852 (s), 762 (w). Anal. Calcd for $C_{12}H_8N_2O_3F_4S$: C, 42.85; H, 2.40; N, 8.37. Found C, 42.79, H, 2.35; N, 8.35. Ms m/z = 336 (M^+).

General procedure for the methoxycarbonylation of the pyridazinyltriflates (4a-f).
A mixture of the 3-trifluoromethylsulfonylpyridazine (1 mmol), triethylamine (0.28 ml, 2 mmol), palladium acetate (6 mg, 0.03 mmol), DPPF (34 mg, 0.06 mmol), and MeOH (1.8 ml, 40 mmol) in DMF (4 ml) was flushed with carbon monoxide for 5 min and stirred under a CO atmosphere at room temperature or at 50 °C for 12 h. Ethyl acetate and water were then added. The organic layer was washed with water until neutral, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate) to give the pure compound.

3-Methoxycarbonyl-6-methylpyridazine (5a)
Yield : 62%; mp 92°C. ^{1}H-Nmr ($CDCl_3$) δ 2.81 (3 H, s, CH_3), 4.01 (3H, s, CH_3), 7.45 - 8.11 (2 H, m, arom.). ^{13}C-Nmr ($CDCl_3$) δ 22.6 (CH_3), 53.2 (CH_3), 127.2 (CH), 127.5 (CH), 149.7 (C), 162.7 (CO). Ir (film) ν (cm^{-1}) : 3060 (w), 1719 (s), 1589 (w), 1498 (w), 1355 (m), 1291 (s), 1155 (m). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H: 5.30; H 18.41. Found: C: 55.32; H: 5.52 ; N: 18.31. Ms m/z = 153 (M^+).

3-Methoxycarbonyl-6-phenylpyridazine (5b)
Yield : 86%; mp 69°C. ^{1}H-Nmr ($CDCl_3$) δ 4.10 (3 H, s, CH_3), 7.52- 8.23 (7 H, m, arom.). ^{13}C-Nmr ($CDCl_3$) δ 53.3 (CH_3), 124.0 (CH), 127.6 (CH), 128.1 (CH), 129.2 (CH), 131.0 (CH), 135.3 (C), 149.9 (C), 160.7 (C), 164.7 (CO). Ir (film) ν (cm^{-1}) : 3076 (w), 1726 (s), 1584 (w), 1444 (m), 1300 (m), 1249. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C: 67.28; H: 4.71; N: 13.08. Found C: 67.03; H: 4.83; N: 13.10. Ms m/z = 214 (M^+).

6-(2',4'-Dichlorophenyl)-3-methoxycarbonyl-5-methylpyridazine (5c)
Yield : 49%; mp 105°C. ^{1}H-Nmr ($CDCl_3$) δ 2.30 (3 H, s, CH_3), 4.11 (3H, s, CH_3), 7.33 - 8.13 (4H, m, arom.). ^{13}C-Nmr ($CDCl_3$) δ 18.5 (CH_3), 53.3 (CH_3), 127.6 (CH), 128.6 (CH), 129.6 (CH), 131.5 (CH), 133.7 (C), 134.1 (C), 136.1 (C), 138.4 (C), 150.5 (C), 162.0 (C), 164.6 (CO). Ir (film) ν (cm^{-1}) : 3064 (w), 1749 (m), 1728 (s), 1590 (s), 1590 (m), 1479 (m), 1439 (m), 1391 (m), 1258 (s), 1111 (s), 986 (w), 796 (m). Anal. Calcd for $C_{13}H_{10}N_2O_2Cl_2$: C: 52.55; H: 3.39; N: 9.43. Found C: 52.39; H: 3.52;N: 9.63. Ms m/z = 297 (M^+, 2 x ^{35}Cl), 299 (M^+, ^{35}Cl and ^{37}Cl), 301 (M^+, 2 x ^{37}Cl).

3-Methoxycarbonyl-5-methyl-6-phenylpyridazine (5d)
Yield : 73%; mp 100°C. ^{1}H-Nmr ($CDCl_3$) δ 2.48 (3 H, s, CH_3), 4.09 (3 H, s, CH_3), 7.47 - 8.10 (6H, m, arom.). ^{13}C-Nmr ($CDCl_3$) δ 19.7 (CH_3), 53.1 (CH_3), 128.4 (CH), 129.2 (CH), 129.3 (CH), 136.2 (C), 136.6 (C), 149.5 (C), 163.6 (C), 164.8 (CO). Ir (film) ν (cm^{-1}) : 3057 (w), 1798 (w), 1724 (s), 1438 (m), 1255 (s), 1112 (m), 770 (m). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C: 68.41; H: 5.30; N: 12.27. Found C: 68.35; H: 5.35; N: 12.25. Ms m/z = 228 (M^+).

3-Methoxycarbonyl-4-methyl-6-phenylpyridazine (5e)
Yield : 68%; mp 128°C. ^{1}H-Nmr ($CDCl_3$) δ 2.68 (3 H, s, CH_3), 4.08 (3 H, s, CH_3), 7.53 - 8.17 (6 H, m, arom.). ^{13}C-Nmr ($CDCl_3$) δ 19.7 (CH_3), 52.9 (CH_3), 126.0 (CH), 127.4 (CH), 129.1 (CH), 130.6 (CH), 135.4 (C), 139.7 (C), 150.5 (C), 159.7 (C), 165.5 (CO). Ir (film) ν (cm^{-1}) : 3052 (w), 1788 (w), 1724 (s), 1441 (m), 1055 (s), 790 (m). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C: 68.41; H: 5.30; N: 12.27. Found C: 68.41; H: 5.38; N: 12.52. Ms m/z = 228 (M^+).

6-(4'-Fluorophenyl)-3-methoxycarbonyl-4-methylpyridazine (5f)
Yield : 72%; mp 195°C. ^{1}H-Nmr ($CDCl_3$) δ 2.66 (3 H, s, CH_3), 4.06 (3 H, s, OCH_3), 7.22 (2 H, dd, J_{HH} = 8.6 Hz, J_{HF} = 8.6 Hz), 7.70 (1 H, s, pyridaz.), 8.14 (2 H, dd, J_{HH} = 8.6 Hz, J_{HF} = 5.3 Hz). ^{13}C-Nmr ($CDCl_3$) δ 19.8 (CH_3), 53.0 (CH_3), 116.0 (CH), 116.4 (CH); 125.7 (CH), 129.4 (C), 129.5 (CH), 131.6 (C), 139.9 (C), 150.4 (C), 158.7 (C), 163.4 (d, J_{CF} = 251 Hz, C), 167.1 (C). Ir (film) ν (cm^{-1}) : 3069 (w), 1791 (w), 1720 (s), 1468 (m), 1055 (s). Anal. Calcd for $C_{13}H_{11}N_2O_2F$: C: 63.41; H: 4.50; N: 11.37. Found C: 63.47; H: 4.38; N: 11.52. Ms m/z = 246 (M^+).

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