SYNTHESIS OF 3-ALKYNYLPYRIDAZINES FROM 3-TRIFLUOROMETHANESULFONYLPYRIDAZINES

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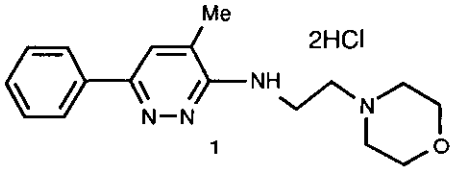
Abstract - An efficient synthesis of 3-alkynylpyridazines starting from the pyridazine triflates using a Pd° cross-coupling reaction is described.

Pyridazines have shown interesting pharmacological activities in the recent years.[1-3] Particularly our studies on 3-aminopyridazines[4,5] led to the development of a new psychotropic pyridazine [minaprine: 3-(3-morpholinoethyl)amino-4-methyl-6-phenylpyridazine dihydrochloride (**1**)]. This compound is an atypical antidepressant, acting mainly through a dual serotoninergic, and dopaminergic mechanism.[5] More recently it was shown to have some weak muscarinic properties.[6]



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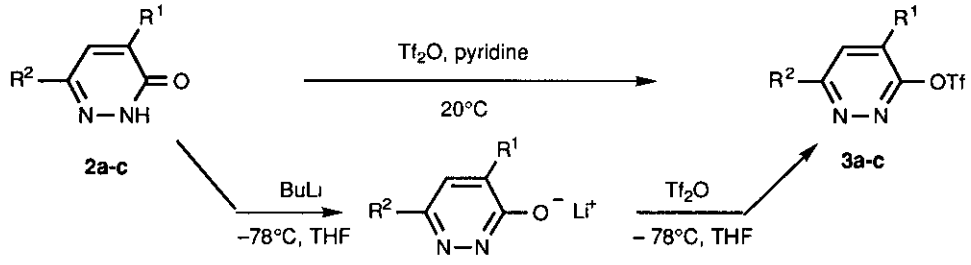
Since the discovery of minaprine, our group has focused much attention on the synthesis of new substituted pyridazines and has found several compounds in the aminopyridazines series which interact selectively with a great number of neurotransmission systems (GABA, serotonin, dopamine, acetylcholine, benzodiazepine).[7-9] Although formation of the oxygen and sulfur analogues of the drug, and in general of O and S substituted pyridazines, have been reported by our group[10] and others,[11-13] there have been only few efficient methods for the direct *C*-functionalization of pyridazines.

Alkylation and arylation of chloropyridazines using Grignard reagents were reported by Ohsawa.[14] Palladium-catalysed cross-coupling reactions of homocyclic halogenated aromatic compounds with monosubstituted acetylenes are well known in synthetic chemistry.[15-17] In the heterocyclic series, the preparation of alkynyl derivatives of pyrimidines, quinolines, isoquinolines and pyridazines using a palladium cross-coupling reaction, and starting from halogenated (iodo and bromo) precursors, has been reported by Yamanaka and coll.[18-20] More recently the same authors proposed the synthesis of ethynyl substituted *N*-heteroaromatic compounds starting

from chloro, bromo and iodo hetero-aromatics.[21] One example on 3-chloropyridazine is given. The reactions are usually conducted in a sealed tube in pure triethylamine, between 70 and 120°C, for several hours. The first preparation of 3-alkynylpyridazines using Pd/CuI cross-coupling reaction, was described by Ohsawa *et al.*[22] in the early 80's. Starting from 3-chloropyridazine, he prepared several 6-substituted aryl- or alkylethynylpyridazines in moderate or even poor yields. In addition, the direct introduction of an alkynyl group into chloropyridazines is limited to the use of phenylacetylene or alkylacetylenes. Recently, it has been shown that reaction of trifluoromethanesulfonyl heteroaromatics with organostannanes,[23-27] organozinc[28-29] reagents, organoboron[30-32] reagents and alkenes[33] in the presence of palladium catalysts gave a straightforward introduction of different substituents into pyrimidines, indoles, cephalosporines, quinolines or isoquinolines. The lack of mild reaction conditions, in the pyridazines series, is a severe limitation for the preparation of sensitive functionalized alkynes. Since iodopyridazines and bromopyridazines are not easily accessible and chloropyridazine does not give satisfactory results in the cross-coupling reactions, we focused our attention on the use of trifluoromethanesulfonylpyridazines (pyridazine triflates) as starting materials for the preparation of substituted alkynylpyridazines. To our knowledge, there is no report for the preparation of pyridazine triflates and their use in the palladium cross-coupling reactions in the literature.

In this paper, we present a synthesis of 3-alkynylpyridazines using a palladium cross-coupling catalysed reaction between 3-trifluoromethanesulfonylpyridazines and several terminal substituted alkynes. The reaction is of general application and can be used with various, differently substituted, pyridazines .



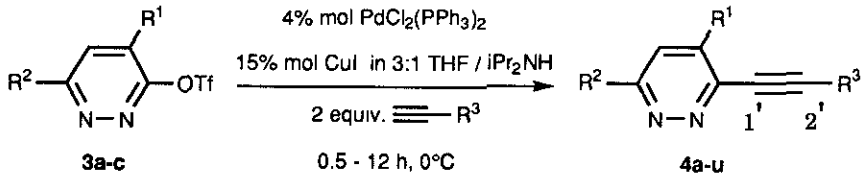
Scheme 1

The pyridazine triflates (**3a-c**) were easily prepared in multigram quantities either (Scheme 1) by reaction of triflic anhydride on the pyridazinone in pyridine at room temperature (**3a-c**) or by action of *n*BuLi in THF at – 78°C followed by a slow addition of triflic anhydride (**3a**). The compounds (**3a-c**) were obtained after flash chromatography as white solids in respectively 77, 90 and 82% yields. They are air stable and can be stored without decomposition at 0°C. When compounds (**3a-c**) were treated under argon at 0°C with 2 equivalents of R^3–C≡CH (Scheme 2) in presence of $Pd(PPh_3)_2Cl_2$ (5% mol), CuI (10% mol) in a 3/1 mixture of THF/iPr_2NH, a rapid reaction occurred and compounds (**4a-u**) were obtained in good yields (see Table).

Table: Coupling of functionalized alkynes with 3-trifluoromethanesulfonylpyridazines in the presence of $Pd(PPh_3)_2Cl_2$

3	R^1	R^2	4	R^3	Time [a]	Yield (%)	mp (°C)	^{13}C nmr C-1' / C-2'
a	Me	Ph	**a**	$-CH_2OH$	5 h	88	139	96.7 ; 81.0
			b	$-SiEt_3$	1.5 h	83	97	101.5 ; 100.8
			c	$-C(Me)_2OH$	3 h	80	166	102.5 ; 80.0
			d	$-CH_2OtBDPS$	3 h	90	105	95.7 ; 80.5
			e	$-C(OH)(CH_2)_5$	4 h	95	138	102.3 ; 79.6
			f	$-CH_2NHtBOC$	2 h	94	decomp.	94.3 ; 79.8
			g	$-CH(OEt)_2$	3 h	95	83	91.5 ; 80.3
b	H	Ph	**h**	$-CH_2OH$	6 h	71	decomp.	93.2 ; 81.7
			i	$-SiEt_3$	2 h	73	98	102.2 ; 98.2
			j	$-C(Me)_2OH$	3 h	92	120	99.7 ; 78.8
			k	$-CH_2OtBDPS$	4 h	82	116	87.5 ; 81.5
			l	$-C(OH)(CH_2)_5$	1.5 h	96	125	98.5 ; 80.5
			m	$-CH_2NHtBOC$	3 h	89	decomp.	89.0 ; 81.5
			n	$-CH(OEt)_2$	3h	83	117	89.0 ; 81.5
c	H	Me	**o**	$-CH_2OH$	6 h	75	decomp.	93.0 ; 80.7
			p	$-SiEt_3$	5 h	89	50	101.9 ; 97.1
			q	$-C(Me)_2OH$	3 h	88	115	98.6 ; 78.2
			r	$-CH_2OtBDPS$	5 h	89	---	91.6 ; 81.7
			s	$-C(OH)(CH_2)_5$	6 h	95	146	97.7 ; 80.4
			t	$-CH_2NHtBOC$	4 h	82	decomp.	89.9 ; 81.5
			u	$-CH(OEt)_2$	6 h	78	56	88.0 ; 81.5

The reaction was complete after 30 min to 6 h and the product was isolated in pure form after flash chromatography on silica gel. In all cases the reaction was extremely clean and no side products were detected. All compounds were characterized by ^1H, ^{13}C nmr, ms, ir, uv and microanalysis. The mass spectra shows the expected molecular ion peak, the ir spectra shows a typical absorption band in the region ν = 2340-2360 cm^{-1} due to the alkyne functionality and the ^{13}C nmr spectra shows the presence of two sp carbons at 80 - 100 ppm.



Scheme 2

We observed that when an electron withdrawing substituent was used (e. g., $R^3 = CO_2Me$, CH_2OCOPh, phthalimide), there was no reaction and the corresponding alkynylpyridazine was not obtained. In order to compare the reactivity of the 3-pyridazine triflates with that of the 3-chloropyridazines, 3-chloro-4-methyl-6-phenyl-pyridazine was submitted to the same reaction conditions ($HO(Me)_2CC{\equiv}CH$, $Pd(PPh_3)_2Cl_2$, CuI, THF/iPr_2NH) as described above. No product was formed (tlc) after several hours. Next, the reaction mixture was heated at reflux of THF under argon for 12 h. The alkynylpyridazine (**4c**) was isolated in only 33% yield (comparing to the 80% yield obtained from the triflate (**3a**)). This experiment proves the efficiency of our new preparation of alkynylpyridazines from trifluoromethanesulfonylpyridazines.

EXPERIMENTAL

Triflic anhydride was prepared from triflic acid using a known procedure.[34] Melting points were determined on a Gallenkampp Melting Point Apparatus and are uncorrected. ^1H nmr (200 MHz) spectra were recorded in $CDCl_3$ solutions on a Bruker WP 200 SY spectrometer. The residual $CHCl_3$ present in $CDCl_3$ was used as internal standard at 7.27 ppm. All chemical shifts are quoted in ppm on the δ scale with all coupling constants expressed in Hertz (Hz). ^{13}C nmr (50 MHz) spectra were recorded on the same instrument with $CDCl_3$ ($\delta = 77.00$) as reference. Microanalyses were performed at the Service de Microanalyse de l'Université Louis Pasteur de Strasbourg. Low resolution mass spectra were recorded on a LKB 9000S mass spectrometer. Ir spectra were recorded on a Bruker IFP 25. Uv spectra were recorded on a Uvikon 810 spectrometer. THF was distilled from sodium/benzophenone ketyl under N_2 prior to use. Diisopropylamine and pyridine were distilled on KOH under N_2 prior to use. All reactions were performed in an oven (140°C) dried glassware under an inert atmosphere of Ar. Tlc were performed on plates pre-coated with Kieselgel $60F_{254}$, visualisation being either by a uv lamp, 5% $KMnO_4$ solution in water, iodine vapor, 5% solution of phosphomolybdic acid in ethanol or cerium (IV) sulfate / ammonium molybdate (VI) tetrahydrate / H_2SO_4 10% reagent followed by heating to ca. 150°C on a hot plate. Column chromatography was performed at the bench using

Kieselgel 60 (40-63 mm mesh, Merck 9385). BuLi was purchased from Aldrich and titrated with *N*-pivaloyl-*o*-toluidine.[35] All reagents were of commercial quality. Triethylsilylacetylene, propargyl alcohol, 1,1–dimethyl–2–propyne-1-ol, propargyl aldehyde diethyl acetal, 1–ethynyl–1–cyclohexanol were commercialy available. *t*-Butyldiphenylsilyloxy–2–propyne, *t*-Butoxycarbonylamino–2–propyne and the pyridazinones (**3a–c**) were prepared according to known procedures.[36-37]

3-Trifluoromethanesulfonylpyridazines (3) : General Procedures :

Method A : 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 (26.1 mmol, 4.4 ml) 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 the appropriate solvent (**3a** : Et_2O / CH_2Cl_2 / hexane, 10 : 20 : 70, **3b** : Et_2O / CH_2Cl_2 / hexane, 10 : 10 : 80, **3c** : Et_2O CH_2Cl_2 / hexane, 40 : 30 : 30).
Method B : In a two-necked, round bottomed flask were introduced under argon, the pyridazinone (37.7 mmol) and distilled THF (140 ml). The solution was cooled to –78°C. *n*BuLi (37.7 mmol) was slowly added via a syringe and the mixture was stirred at –78°C for 30 min. Triflic anhydride (37.7 mmol, 6.36 ml) was slowly added. After the addition was complete, the solution was stirred for another 10 min at –78°C. The reaction was quenched with brine (200 ml) and the triflate extracted with Et_2O (3 x 50 ml). The combined organic layers were washed with water (2 x 100 ml) and dried over anhydrous Na_2SO_4 . Filtration on Celite and evaporation *in vacuo* followed by flash chromatography (see solvent above), yielded the pure trifluoromethane-sulfonylpyridazines.

4-Methyl-6-phenyl-3-trifluoromethanesulfonylpyridazine (3a) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 10 : 20 : 70, R_f : 0.44, yield : 72%, white solid, mp 147°C. *Anal.* Calcd for $C_{12}H_9N_2O_3F_3S$: C, 45.28 ; H, 2.85 ; N, 8.80. Found : C, 45.49 ; H, 3.00 ; N, 8.91. Ms (15 eV) *m/z* (%) = 318 (100), 129 (58). Ir ($CHCl_3$) : ν = 2980 w, 1680 vw, 1585 m, 1415 s, 1380 m, 1205 vs, 1125 s, 1060 vw, 1040 vw, 1000 vw. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.04 (m, 2H, arom.), 7.87 (s, 1H, H pyridaz.), 7.52 (m, 2H, arom.), 2.49 (s, 3H, Me). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 160.57, 134.55, 131.98, 130.71, 129.38, 129.15, 127.28, 121.79, 15.69. Uv (MeCN) : λ = 252 nm ; $\mathcal{E}$ = 15815 ; λ = 201 nm ; $\mathcal{E}$ = 27860.

6-Phenyl-3-trifluoromethanesulfonylpyridazine (3b) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 10 : 10 : 80, R_f : 0.19, yield : 82%, white solid, mp 110°C. *Anal.* Calcd for $C_{11}H_7N_2O_3F_3S$: C, 43.43 ; H, 2.32 ; N, 9.21. Found : C, 43.30 ; H, 2.21 ; N, 9.03. Ms (15 eV) :

m/z (%) = 304 (26), 115 (100). Ir ($CHCl_3$) : ν = 3015 m, 1632 m , 1375 m, 1117 w, 1050 w. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.09 (m, 2H, arom.), 7.83 (AB system, 2H pyridaz., J_{AB} = 9 Hz, $\Delta\nu$ = 53 Hz), 7.54 (m, 3H, arom.). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 160.60, 134.26, 132.45, 130.91, 129.21, 128.72, 127.25, 125.80. Uv (MeCN) : λ = 255 nm ; $\mathcal{E}$ = 18020 λ = 196 nm ; $\mathcal{E}$ = 29815.

6-Methyl-3-trifluoromethanesulfonylpyridazine (3c) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 40 : 30 : 30, R_f : 0.46, yield : 90%, white solid, mp 59°C. *Anal.* Calcd for $C_6H_5N_2O_3F_3S$: C, 29.76 ; H, 2.08 ; N, 11.57. Found : C, 29.98 ; H, 1.89 ; N, 11.51. Ms (15 eV) : m/z (%) = 242 (100), 53 (54). Ir ($CHCl_3$) : ν = 3019 m, 1632 m , 1427 m, 1375 vw, 1214 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 7.47 (AB system, 2H pyridaz., J_{AB} = 9 Hz, $\Delta\nu$ = 48 Hz), 2.76 (s, 3H, Me). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 161.99, 131.72, 121.70, 120.29, 21.56. Uv (MeCN) : λ = 253 nm ; $\mathcal{E}$ = 14103 : λ = 191 nm ; $\mathcal{E}$ = 9074.

3- Alkynylpyridazines (4) : General Procedure:

In a 25 ml two-necked, round bottomed flask are introduced at 0°C under argon the triflate (0.628 mmol) in anhydrous THF (7 ml). The alkyne (1.57 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg) and CuI (18 mg) are respectively added. Freshly distilled diisopropylamine (2.5 ml) is then added quickly. The solution turns from orange to black. The reaction is followed by tlc (see each individual case). The solution is stirred at 0°C for 1 h, then at room temperature for the time indicated in the Table. The brown solution is poured into water (50 ml), then extracted three times with CH_2Cl_2 (30 ml). The combined organic layers are washed with brine (30 ml), dried over anhydrous sodium sulfate and treated with charcoal. Filtration on Celite and evaporation *in vacuo*, yields the desired alkynylpyridazine which is flash chromatographed eluting with the appropriate solvent (see experimental details).
Compounds (**4f**, **4h**, **4m**, **4o**, **4p**, **4t**) were prepared according to the following modified procedure. After the reaction was completed (tlc), the crude mixture was directly evaporated *in vacuo* without any aqueous work up. Then the solid was dissolved and chromatographed on silica gel, affording the pure corresponding alkynylpyridazine.

3-(3-Hydroxy-1-propynyl)-4-methyl-6-phenylpyridazine (4a) : chromatography solvent Et_2O / CH_2Cl_2, 80 : 20, R_f : 0.46, yield : 88%, light brown solid, mp 139°C. *Anal.* Calcd for $C_{14}H_{12}N_2O$: C, 74.98 ; H, 5.39 ; N, 12.49. Found : C, 74.25 ; H, 5.30 ; N, 12.17. Ms (15 eV) : m/z (%) = 224 (100), 196 (16), 165 (11), 152 (18), 128 (7), 102 (90). Ir ($CHCl_3$) : ν = 3062 m, 3318 bm, 3005 m, 2925 w, 2868 w, 2362 w, 1587 m, 1451 m, 1396 s, 1262 w, 1024 m, 955 w, 898 w. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.06 (m, 2H, arom.), 7.67 (s, 1H, H pyridaz.), 7.51 (m, 3H, arom.), 4.66 (s, 2H, CH_2-O), 2.50 (s, 3H, Me pyridaz.). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 157.2, 147.0, 140.1, 135.9, 130.2, 129.0, 127.2, 123.6, 96.0, 51.4, 29.7, 19.2. Uv (CH_2Cl_2) :λ = 270nm ;$\mathcal{E}$ = 32823.

3-(2-Triethylsilylethynyl)-4-methyl-6-phenylpyridazine (4b) : chromatography solvent AcOEt / CH_2Cl_2 / hexane, 10 : 10 : 80, R_f : 0.30, yield : 83%, light brown solid, mp 97°C. *Anal.* Calcd for $C_{19}H_{24}N_2Si$: C, 73.97 ; H, 7.84 ; N, 9.08. Found : C, 74.15 ; H, 8.01 ; N, 8.97. Ms (70eV) : *m/z* (%) = 308 (24), 280 (100), 251 (49), 223 (24), 93 (20), 45 (15). Ir ($CHCl_3$) : ν = 3016 w, 2958 m, 2876 w, 2363 w, 1586 w, 1450 w, 1392 m, 1378 m, 1226 s, 1004 w, 975 vw, 897 vw. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.07 (m, 2H, arom.), 7.66 (s, 1H, H pyridaz.), 7.50 (m, 3H, arom.), 2.50 (s, 3H, Me), 1.09 (t, ^3J = 7.5 Hz, 9H, 3 Me), 0.78 (q, ^3J = 7.5 Hz, 6H). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 156.01, 146.82, 140.24, 135.79, 129.90, 128.80, 126.99, 123.20, 101.50, 100.78, 19.24, 7.36, 4.06. Uv (MeCN) : λ = 276 nm ; $\mathcal{E}$ = 31173 ; λ = 194 nm ; $\mathcal{E}$ = 34259.

3-(-3,3-Dimethyl-3-hydroxy-1-propynyl)-4-methyl-6-phenylpyridazine (4c) : chromatogra-phy solvent Et_2O / MeOH, 90 : 10, R_f : 0.66, yield : 80%, light yellow solid, mp 166-167°C. *Anal.* Calcd for $C_{16}H_{16}N_2O$: C, 76.17 ; H, 6.39 ; N, 11.10. Found : C, 76.17 ; H, 6.63 ; N, 11.17. Ms (15 eV) *m/z* (%) = 252 (100), 237 (78), 209 (36), 195 (27), 165 (17), 107 (22), 102 (39). Ir ($CHCl_3$) : ν = 3595 m, 3343 bm, 3064 w, 2987 s, 2932 m, 2862 w, 2235 w, 1588s, 1451 s, 1396 s, 1328 m, 1269 m, 1167 s, 1114 w, 963 m, 897 m, 693 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.04 (m, 2H, arom.), 7.62 (s, 1H, H pyridaz.), 7.48 (m, 3H, arom.), 3.62 (s, 1H, OH), 2.45 (s, 3H, Me pyridaz.), 1.71 (s, 6H, 2 Me). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 156.96, 147.11, 140.07, 135.91, 130.04, 128.92, 127.13, 123.43, 102.62, 80.05, 65.47, 31.17, 19.15. Uv (MeCN) : λ = 270 nm ; $\mathcal{E}$ = 43807 : λ = 198 nm ; $\mathcal{E}$ = 41972.

3-(3-*t*-Butyldiphenylsilyloxy-1-propynyl)-4-methyl-6-phenylpyridazine (4d) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 20 : 20 : 60, R_f : 0.35, light yellow solid, yield : 90%, mp 105°C. *Anal.* Calcd for $C_{30}H_{30}N_2OSi$: C, 77.88 ; H, 6.63 ; N, 6.05. Found : C, 77.85 ; H, 6.55 ; N, 6.00. Ms (15 eV) : *m/z* = 462 (15), 405 (100). Ir ($CHCl_3$) : ν = 3072 w, 3013 m, 2943 m, 2860 m, 2343 m, 1584 m, 1396 s, 1260 w, 1219 m, 1108 s, 1085 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.09 (m, 2H, arom.), 7.80 (m, 3H, arom.), 7.65 (s, 1H, H pyridaz.), 7.45 (m, 10H, 2 Ph), 4.70 (s, 2H, CH_2-O), 2.41 (s, 3H, Me), 1.15 (s, 9H, *t*-Bu). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 156.79, 147.09, 139.98, 135.52, 132.79, 129.91, 128.81, 127.68, 127.02, 123.20, 95.71, 80.49, 53.03, 26.60, 19.05. Uv (MeCN): λ = 274 nm ; $\mathcal{E}$ = 24911.

3-(3-Cyclohexyl-3-hydroxy-1-propynyl)-4-methyl-6-phenylpyridazine (4e) : chromatography solvent CH_2Cl_2 / hexane, 90 : 10, R_f : 0.52, light brown solid, yield : 95%, mp 138°C. *Anal.* Calcd for $C_{19}H_{20}N_2O$: C, 78.05 ; H, 6.89 ; N, 9.58. Found : C, 77.90 ; H, 6.75 ; N, 9.45. Ms (15eV) : *m/z* = 292 (64), 249 (42), 22 (98), 81 (47), 69 (100). Ir ($CHCl_3$) : ν = 3589 m, 3356 bm, 3015 w, 2939 s, 2859 m, 2226 vw, 1588 m, 1450 m, 1396 s, 1380, m, 1328 w, 1264 w, 1069 w, 964 m, 904 w. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.08 (m,1H, arom.), 7.66 (s, 1H, H pyridaz.), 7.52 (m, 3H, arom.), 2.75 (s, 1H, OH), 2.50 (s, 3H, Me), 2.00-2.17 (m, 2H, cyclohexyl), 1.60-1.80 (m, 7H, cyclohexyl), 1.45-1.70 (m, 1H, cyclohexyl). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 156.93, 147.17, 140.15,

135.82, 130.01, 128.87, 127.08, 123.44, 102.35, 79.57, 68.97, 39.63, 25.11, 23.25, 19.28. Uv (CH_2Cl_2) : λ = 274 nm ; $\mathcal{E}$ = 21197.

3-(3-*t*-Butoxycarboxylamino-1-propynyl)-4-methyl-6-phenylpyridazine (4f) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 60 : 20 : 20, R_f : 0.39, yield : 94%, light brown solid, mp 160°C (decomp.) . Ms (15 eV) : *m/z* = 323 (3), 267 (100), 223 (10), 211 (9). Ir ($CHCl_3$) : ν = 3456 m, 2983 m, 2361 w, 1714 s, 1588 w, 1502 s, 1451 m, 1395 m, 1368 m, 1248 m, 1163 s, 1051 w, 898 w, 857 w. ^1H nmr (200 MHz, $CDCl_3$) : δ = 7.97 (m, 2H, arom.), 7.55 (s, 1H, H pyridaz.), 7.41 (m, 3H, arom.), 5.42 (br s, 1H, NH), 4.22 (d, 2H, ^3J = 5 Hz, CH_2-N), 2.37 (s, 3H, Me), 1.43 (s, 9H, *t*Boc). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 156.73, 155.48, 146.95, 140.07, 135.71, 129.87, 128.75, *126.96, 123.27, 94.26, 79.82, 78.29, 31.35, 28.17, 18.95.* Uv (MeCN) : λ = 272 nm ; $\mathcal{E}$ = *21965* ; λ = 194 nm ; $\mathcal{E}$ = 23095.

3-(3,3-Diethoxy-1-propynyl)-4-methyl-6-phenylpyridazine (4g) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 25 : 20 : 55, R_f : 0.25, yield : 95%, light brown solid, mp 83°C. *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95 ; H, 6.80 ; N, 9.45. Found : C, 72.75 ; H, 6.86 ; N, 9.39. Ms (70 eV) : *m/z* (%) = 296 (4), 252 (51), 223 (100), 102 (29), 93 (10). Ir ($CHCl_3$) : ν = 3024 m, 2981 m, 2363 w, 1538 w, 1450 m, 1406 s, 1326 w, 1140 s, 1051 s, 1012 m. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.07 (m, 2H, arom.), 7.67 (s, 1H, H pyridaz.), 7.52 (m, 3H, arom.), 5.60 (s, 1H, CH), 3.80 (ABX_3 system, 4H, J_{AB} = 9.5 Hz, J_{BX} = 7Hz, J_{AX} = 7Hz, $\Delta\nu$ = 77.5 Hz). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 156.96, 146.41, 140.27, 135.51, 129.96, 128.80, 126.95, 123.34, 91.90, 91.48, 80.25, 61.12, 19.03, 14.99. Uv (MeCN) : λ = 272 nm ; $\mathcal{E}$ = 24308 : λ = 196 nm ; $\mathcal{E}$ = 25099.

3-(3-Hydroxy-1-propynyl)-6-phenylpyridazine (4h) : chromatography solvent CH_2Cl_2 / AcOEt, 35 : 65, R_f : 0.36, yield : 71%, yellow solid, mp 115°C (decomp). Ms (15 eV) : *m/z* (%) = 210 (100), 182 (9), 153 (18), 102 (14). Ir ($CHCl_3$) : ν = 3602 m, 3343 bm, 3015 m, 2868 vw, 2362 w, 1536 m, 1451 m, 1407 s, 1288 m, 1218 m, 1119 w, 1035 m, 1014 m, 949 w, 850 m, 841 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.05 (m, 2H, arom.), 7.71 (AB system, 2H pyridaz., J_{AB} = 10 Hz, $\Delta\nu$ = 41 Hz), 7.50 (m, 3H, arom.), 4.64 (s, 2H, CH_2-O), 4.34 (s, 1H, OH). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 157.34, 145.67, 135.80, 131.3, 130.34, 129.03, 127.13, 123.16, 93.23, 81.73, 51.18. Uv (CH_2Cl_2) : λ = 270 nm ; $\mathcal{E}$ = 27453.

3-(2-Triethylsilyl-1-ethynyl)-6-phenylpyridazine (4i) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 5 : 35 : 60, R_f : 0.45, yield : 73%, light yellow solid, mp 98°C. *Anal.* Calcd for $C_{18}H_{22}N_2Si$: C, 73.42 ; H, 7.53 ; N, 9.51. Found : C, 73.41 ; H, 7.69 ; N, 9.48. Ms (15 eV) : *m/z* (%) = 294 (34), 266 (100), 237 (10). Ir ($CHCl_3$) : ν = 3064 w, 3004 m, 2959 s, 2876 m, 2361 w, 1538 m, 1490 w, 1450 m, 1403 s, 1276 m, 1235 m, 1112 w, 1013 m, 975 w, 846 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.08 (m, 2H, arom.), 7.71 (AB system, 2H, pyridaz., J_{AB} = 10 Hz, $\Delta\nu$ = 38 Hz), 7.52 (m, 3H, arom.), 1.08 (t, ^3J = 7.5 Hz, 9H, 3 Me), 0.75 (q, ^3J = 7.5 Hz, 6H, 3 CH_2). ^{13}C nmr (50

MHz, $CDCl_3$) : δ = 156.92, 146.06, 135.62, 130.15, 128.87, 127.01, 122.73, 102.05, 98.15, 73.37. Uv (MeCN) : λ = 278 nm ; $\mathcal{E}$ = 27518 : λ = 196 nm ; $\mathcal{E}$ = 30221.

3-(3,3-Dimethyl-3-hydroxy-1-propynyl)-6-phenylpyridazine (4j) : chromatography solvent Et_2O / CH_2Cl_2, 80 : 20, R_f : 0.34, yield : 92%, white solid, mp 120-121°C. *Anal.* Calcd for $C_{15}H_{14}N_2O$: C, 75.61 ; H, 5.92 ; N, 11.75. Found : C, 75.39 ; H, 5.94 ; N, 11.67. Ms (15 eV) : *m/z* (%) = 238 (100), 223 (38), 195 (16), 167 (10). Ir ($CHCl_3$) : ν = 3595 w, 3360 w, 2988 m, 2934 w, 2363 w, 2237 w, 1538 m, 1452m 1407 s, 1290 m, 1166 m, 1114 w, 961 m, 909 m, 850 m. ^{1}H nmr (200 MHz, $CDCl_3$) : δ = 8.09 (m, 2H, arom.), 7.90 (AB system, 2H pyridaz., J_{AB} = 10 Hz, $\Delta\nu$ = 39 Hz), 7.52 (m, 3H, arom.), 2.61 (s, 1H,OH), 1.70 (s, 6H, 2 Me). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 157.08, 156.01, 146.04, 132.18, 130.07, 128.97, 127.07, 122.95, 99.70, 78.77, 65.30, 31.05. Uv (CH_2Cl_2) : λ = 270 nm ; $\mathcal{E}$ = 21127.

3-(3-*t*-Butyldiphenylsilyloxy-1-propynyl)-6-phenylpyridazine (4k) : chromatography solvent AcOEt / CH_2Cl_2 / hexane, 10 : 10 : 80, R_f : 0.28, yield : 82%, light brown solid, mp 116°C. *Anal.* Calcd for $C_{29}H_{28}N_2OSi$: C, 77.64 ; H, 6.29 ; N, 6.24. Found : C, 77.50 ; H, 6.30 ; N, 6.13. Ms (15 eV) : *m/z* (%) = 448 (3), 391 (100). Ir ($CHCl_3$) : ν = 3073 w, 3007 w, 2932 m, 2860 m, 2347 vw, 1602 w, 1536 w, 1407s, 1370 m, 1225 s, 1206 s, 1112 s, 1090 s, 998 w, 850 m, 803 m. ^{1}H nmr ($CDCl_3$, 200 MHz) : δ = 8.11 (m, 3H, arom.), 7.79 (m, 4H, arom., H pyridaz.), 7.57—7.40 (m, 10H, 2 Ph.), 4.65 (s, 2H, CH_2-O), 1.12 (s, 9H, 3 Me). ^{13}C nmr ($CDCl_3$, 50 MHz) : δ =157.05, 146.02, 135.65, 132.68, 130.20, 129.75, 129.09, 127.65, 127.04, 122.84, 92.57, 81.82, 53.00, 26.66, 19.13. Uv (MeCN) : λ = 270 nm ; $\mathcal{E}$ = 29962.

3-(3-Cyclohexyl-3-hydroxy-1-propynyl)-6-phenylpyridazine (4l) : chromatography solvent AcOEt / CH_2Cl_2, 25 : 75, R_f : 0.43, yield : 96%, white solid, mp 125°C. *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67 ; H, 6.52 ; N, 10.06. Found : C, 77.57 ; H, 6.55 ; N, 9.92. Ms (15 eV) : *m/z* (%) = 278 (100), 250 (25), 235 (16), 221 (10), 207 (45), 194 (10). Ir ($CHCl_3$) : 3591 w, 3556 bw, 3006 m,2939 s, 2859 m, 2228 vw, 1538 m, 1451 m, 1406 s, 1290 w, 1227 m, 1069 w, 964 m, 850 m. ^{1}H nmr (200 MHz, $CDCl_3$) : δ = 8.08 (m, 2H, arom.), 7.69 (AB system, 2H pyridaz., J_{AB} = 10 Hz, $\Delta\nu$ = 41 Hz), 7.53 (m, 3H, arom.), 2.99 (s, 1H, OH), 2.10 (m, 4H, CH_2), 1.74 (m, 4H, CH_2-), 1.34 (m, 2H,-CH_2-). ^{13}C nmr (50 MHz, $CDCl_3$) :δ = 156.93, 146.08, 139.15, 138.91, 127.03, 123.00, 98.51, 80.72, 68.71, 39.5, 29.55, 25.04, 23.11. Uv (CH_2Cl_2) : λ = 270 nm ; $\mathcal{E}$ = 24348.

3-(3-*t*-Butoxycarboxylamino-1-propynyl)-6-phenylpyridazine (4m) : chromatography solvent, Et_2O / CH_2Cl_2 / hexane, 50 : 30 : 20, R_f : 0.40, yield : 89%, light brown solid, mp 115°C. *Anal.* Calcd for $C_{18}H_{19}N_3O_2$: C, 69.89 ; H, 6.19 ; N, 13.58. Found : C, 69.78 ; H, 6.26 ; N, 12.89. Ms (15 eV) : *m/z* (%) = 309 (2), 279 (6), 253 (100), 209 (15). Ir ($CHCl_3$) : 3456 m, 2983 m, 2361 w, 1714 s, 1537 w, 1502 s, 1451 m, 1407 m, 1368 m, 1247 m, 1163 s, 1050 w, 976 w, 915 w, 850 m. ^{1}H nmr (200 MHz, $CDCl_3$) : δ = 8.02 (m, 2H, arom.), 7.74 (AB system, 2H pyridaz., J_{AB} =

10 Hz, $\Delta\nu$ = 40 Hz), 7.45 (m, 3H, arom.), 5.36 (br s, 1H, NH), 4.22 (d, 2H, ^3J = 5 Hz, CH_2-N), 1.43 (s, 9H, *t*Boc). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 157.14, 155.26, 145.93, 135.65, 130.22, 129.85, 128.95, 127.05, 122.86, 90.90, 80.07, 79.72, 31.19, 28.26. Uv (MeCN) : λ = 270 nm ; $\mathcal{E}$ = 28095 : λ = 194 nm ; $\mathcal{E}$ = 29524.

3-(3,3-Dimethoxy-1-propynyl)-6-phenylpyridazine (4n) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 20 : 30 : 50, R_f : 0.27, yield : 83%, light brown solid, mp 117°C. *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32 ; H, 6.42 ; N, 9.92 : Found : C, 72.25 ; H, 6.36 ; N, 9.81. Ms (15 eV) : *m/z* (%) = 238 (100), 209 (54), 197 (4). Ir ($CHCl_3$) : ν = 2982 m, 2931 w, 2888 w, 2361 w, 1586 m, 1450 m, 1394 s, 1327 m, 1258 w, 1114 m, 1051 s, 1011 w, 916 w, 898 w. ^1H nmr (200 MHz, $CDCl_3$) : δ = 8.09 (m, 2H, arom.), 7.75 (AB system, 2H pyridaz., J_{AB} = 8 Hz, $\Delta\nu$ = 24 Hz), 7.50 (m, 3H, arom.), 5.56 (s, 1H, CH), 3.68 (ABX_3 system, 4H, J_{AB} = 9.5 Hz, J_{BX} = 7 Hz, J_{AX} = 7 Hz, $\Delta\nu$ = 77.5 Hz), 1.29 (t, 6H, ^3J= 5 Hz, 2 Me). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 157.25, 145.27, 135.39, 130.28, 130.05, 128.89, 126.99, 122.77, 91.41, 88.75, 81.51, 61.20, 14.91. Uv (CH_2Cl_2) : λ = 272 nm ; $\mathcal{E}$ = 23478.

3-(3-Hydroxy-1-propynyl)-6-methylpyridazine (4o) : chromatography solvent AcOEt / CH_2Cl_2 / MeOH, 75 : 20 : 5, R_f : 0.39, light brown solid, yield : 75%, mp 165°C (decomp.). *Anal.* Calcd for $C_8H_8N_2O$: C, 64.85 ; H, 5.44 ; N, 18.91. Found : C, 64.71 ; H, 5.18 ; N, 18.80. Ms (15eV) : *m/z* (%) = 148 (100), 119 (10), 91 (98), 77 (23), 65 (38), 51 (37). Ir ($CHCl_3$) : ν = 3602 m, 3333 bm, 2998 m, 2867 w, 2362 w, 1543m, 1419 s, 1381 w, 1270 m, 1095 m, 1033 m, 949 m, 838 m. ^1H nmr (200 MHz, DMSO-d_6) : δ = 7.61 (AB system, 2H pyridaz., J_{AB} = 7.5 Hz, $\Delta\nu$ = 21 Hz), 5.54 (t, 1H, ^3J = 6 Hz, OH), 4.34 (d, 2H, ^3J = 6 Hz, CH_2-O), 2.62 (s, 3H, Me). ^{13}C nmr (50 MHz, DMSO-d_6) : δ =158.46, 144.95, 129.36, 126.67, 93.06, 80.72, 49.25, 21.55. Uv (CH_2Cl_2) : λ = 240 nm ; $\mathcal{E}$ = 15346.

3-(2-Triethylsilyl-1-ethynyl)-6-methylpyridazine (4p) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 30 : 30 : 40, R_f : 0.31, yield : 89%, white solid, mp 50°C. Ir ($CHCl_3$) : ν = 2959 s, 2876 m, 2361 w, 1544 m, 1458 m, 1414 s, 1252 s, 1087 m, 1007 m, 975 w, 845 m. ^1H nmr (200 MHz, $CDCl_3$) : δ = 7.34 (AB system, J_{AB} = 10 Hz, $\Delta\nu$ = 36 Hz), 2.68 (s, 3H, Me), 0.99 (t, ^3J = 7.5 Hz, 9H, 3 Me), 0.67 (q, ^3J = 7.5 Hz, 6H, 3 CH_2). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 158.24, 145.61, 129.67, 125.80, 101.98, 97.07, 22.22, 7.25, 4.03. Uv (MeCN) : λ = 242 nm ; $\mathcal{E}$ = 13097.

3-(3,3-Dimethyl-3-hydroxy-1-propynyl)-6-methylpyridazine (4q) : chromatography solvent Et_2O / MeOH, 90 : 10, R_f : 0.44, yield : 88%, light brown solid, mp 115°C. *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16 ; H, 6.86 ; N, 15.89 ; Found : C, 68.14 ; H, 6.70 ; N, 15.74. Ms (15 eV) : *m/z* (%) =176 (79), 161 (100), 133 (41), 119 (64), 105 (11), 93 (10). Ir ($CHCl_3$) : ν = 3594 m, 3354 bm, 2988s, 2870 w, 2362 w, 2246 w, 1541 m, 1419 s, 1366 m, 1332 m, 1166 m, 1114 w, 1030 w, 961 m, 909 m, 838 s, 671 s, 504 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 7.35 (AB system, 2H pyrida.,

J_{AB} = 10 Hz, $\Delta\nu$ = 29 Hz), 2.75 (s, 1H, OH), 2.73 (s, 3H, Me pyridaz.), 1.67 (s, 6H, 2 Me). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 158.18, 145.38, 129.53, 126.21, 98.57, 78.21, 64.84, 30.91, 21.95. Uv (MeCN) : λ = 236 nm ; $\mathcal{E}$ = 14537 : λ = 190 nm ; $\mathcal{E}$ = 11383.

3-(3-*t*-Butyldiphenylsilyloxy-1-propynyl)-6-methylpyridazine (4r) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 50 : 20 : 30, R_f : 0.35, yield : 89%, orange oil. *Anal.* Calcd for $C_{24}H_{26}N_2OSi$: C, 74.57 ; H, 6.79 ; N 7.25. Found : C, 74.45 ; H, 6.80 ; N, 7.10. Ms (15 eV) : *m/z* (%) = 386 (7), 329 (100), 299 (43), 231 (11), 199 (7). Ir ($CHCl_3$) : ν = 3073 w, 3000 m, 2962 m, 2932 m, 2860 m, 2340w, 1589 w, 1543 w, 1464 w, 1428 s, 1373 w, 1270 w, 1112 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 7.79-7.39 (m, 12H, arom.+ pyridaz.), 4.60 (s, 2H, CH_2-O), 2.72 (s, 3H, Me), 1.09 (s, 9H, *t*Bu). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 158.32, 145.47, 135.57, 132.85, 129.81, 129.29, 127.71, 125.86, 91.63, 81.74, 52.95, 26.64, 22.25, 19.13. Uv (MeCN) λ = 240 nm ; $\mathcal{E}$ = 14936.

3-(3-Cyclohexyl-3-hydroxy-1-propynyl)-6-methylpyridazine (4s) : chromatography solvent AcOEt / CH_2Cl_2, 80 : 20, R_f : 0.33, yield : 95%, white solid, mp 146°C. *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19 ; H, 7.46 ; N, 12.95. Found : C, 72.10 ; H, 7.56 ; N 12.96. Ms (15 eV) : *m/z* (%) = 216 (41), 187 (20), 173 (51), 159 (19), 145 (100), 132 (26). Ir ($CHCl_3$) : ν = 3590 m, 3334 bm, 3001 m, 2940 s, 2860 m, 2362 w, 1583 w, 1543 m, 1446 m, 1418 s, 1341 m, 1260 w, 1154 w, 1067 m, 964 s, 904 m, 837 m, 804 s. ^1H nmr (200 MHz, $CDCl_3$) : δ = 7.36 (AB system, 2H pyridaz., J_{AB} = 9 Hz, $\Delta\nu$ = 31 Hz), 4.15 (s, 1H, OH), 2.66 (s, 3H, Me), 2.06 (m, 4H,- CH_2-), 1.65 (m, 4H, -CH_2), 1.26 (m, 2H, -CH_2-). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 158.21, 145.50, 129.62, 126.15, 97.71, 80.46, 68.51, 39.45, 25.02, 23.03, 22.08. Uv (MeCN) : λ = 240 nm ; $\mathcal{E}$ = 16576 : λ = 200 nm ; $\mathcal{E}$ = 12973.

3-(3-*t*-Butylcarboxylamino-1-propynyl)-6-methylpyridazine (4t) : chromatography solvent Et_2O / CH_2Cl_2, 90 : 10, R_f : 0.28, yield : 82%, light yellow solid, mp 162°C (decomp.). Ir ($CHCl_3$) : ν = 3456 m, 2983 m, 2361 w, 1713 s, 1543 w, 1502 s, 1419 w, 1368 w, 1270 w, 1231 m, 1169 m, 1094 w, 1050 w. ^1H nmr (200 MHz, $CDCl_3$) : δ = 7.33 (AB system, 2H pyridaz., J_{AB} = 9 Hz, $\Delta\nu$ = 26 Hz), 5.27 (br s, 1H, NH), 4.19 (d, 2H, ^3J = 6 Hz, CH_2-N), 2.69 (s, 3H, Me), 1.42 (s, 9H, *t*Boc). ^{13}C nmr (50 MHz, $CDCl_3$) : δ = 158.47, 155.20, 145.39, 129.35, 126.04, 89.85, 80.09, 79.63, 31.11, 28.25, 22.22. Uv (MeCN) : λ = 236 nm ; $\mathcal{E}$ = 14191 : λ = 194 nm ; $\mathcal{E}$ = 12871.

3-(3,3-Diethoxy-1-propynyl)-6-methylpyridazine (4u) : chromatography solvent Et_2O / CH_2Cl_2 / hexane, 70 : 20 : 10, R_f : 0.36, orange solid, yield : 78%, mp 56°C. *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43 ; H, 7.32 ; N, 12.72. Found : C, 65.51 ; H, 7.29 ; N, 12.60. Ms (15 ev) : *m/z* (%) = 220 (1.3), 175 (62), 147 (100), 119 (10), 89 (9), 77 (8). Ir ($CHCl_3$) : ν = 2982 m, 2918 w, 2894 w, 2356 vw, 1545 w, 1417 m, 1329 w, 1266 w, 1114 m, 1052 s, 1012 w, 832 m. ^1H nmr ($CDCl_3$) : δ = 7.34 (AB system, 2H pyridaz., J_{AB} = 8 Hz, $\Delta\nu$ = 24 Hz), 5.45 (s, 1H, C-H), 3.68 (ABX_3 system,

4H, J_{AB} = 9.5 Hz, J_{BX} = 7 Hz, J_{AX} = 7 Hz, $\Delta\nu$ = 77.5 Hz), 2.66 (s, 3H, Me pyrida.), 1.20 (t, 6H, ^3J= 5 Hz, 2 Me). ^{13}C nmr ($CDCl_3$) : δ = 158.70, 144.75, 129.45, 125.89, 91.44, 87.95, 81.42, 61.18, 22.16, 14.88. Uv (MeCN) : λ = 234 nm ; $\mathcal{E}$ = 16079 : λ = 196 nm ; $\mathcal{E}$ = 14978.

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REFERENCES

1. G. Heinisch and H. Frank, In *Progress in Medicinal Chemistry,* Vol. 27 pp. 1-49, ed. by G. P. Ellis and G. B. West © **1990**, Elsevier Science Publishers, B. V.

2. G. Heinisch and H. Kopelent-Frank, In *Progress in Medicinal Chemistry,* Vol. 29, pp. 141-183, ed. by G. P. Ellis and D. K. Luscombe © **1992**, Elsevier Science Publishers, B. V.

3. C.G. Wermuth, Recherches en Chimie Thérapeutique-Potentialités Pharmacologiques et Thérapeutiques des Amino-3 Pyridazines. In *Actualités de Chimie Thérapeutique, 12éme Série,* Sociéte de Chimie Thérapeutique, Paris, **1985**, pp. 3-35.

4. C. G. Wermuth, G. Schlewer, J. J. Bourguignon, G. Maghioros, M. J. Bouchet, C. Moire, J. P. Kan, P. Worms, and K. Biziere, *J. Med. Chem.* **1989**, 32, 528.

5. K. Bizière, J. P. Kan, J. Souilhac, J. P. Muyard, and R. Roncucci, *Arzneim. Forsch. (Drug Res.)*, **1982**, *32 II 8*, 824.

6. P. Worms, J. P. Kan, R. Steinberg, J. P. Terranova, A. Pério, and K. Bizière *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **1989**, *340*, 411.

7. C. G. Wermuth, J. J. Bourguignon, G. Schlewer, J. P. Gies, A. Schoenfelder, A. Melikian, M. J. Bouchet, D. Chantreux, J. C. Molimard, M. Heaulme, J. P. Chambon, and K. Bizière, *J. Med. Chem.*, **1987**, *30*, 239.

8. C. Schumacher, R. Steinberg, J. P. Kan, J. C. Michaud, J. J. Bourguignon, C. G. Wermuth, P. Feltz, P. Worms, and K. Bizière, *Eur. J. Pharmacol.*, **1989**, *166,* 139.

9. K. Bizière, J. J. Bourguignon, J. P. Chambon, M. Heaulme, A. Pério, S. Tebib, and C. G. Wermuth, *J. Pharmac.*, **1987**, *90*, 183.

10. C. G. Wermuth and A. Exinger, *Agressologie,* **1972**, *13*, 285.

11. A. Lespagnol and J. Deprey, *Bull. Soc. Chim. Fr.,* **1962**, *II*, 111.

12. W. G. Overend and L. F. Wiggins, *J. Chem. Soc.,* **1947**, 239.

13. M. Tisler and B. Stanovnik, In *Pyridazines, The Chemistry of Heterocyclic Compounds ed. by O. Castle, Interscience New York*, **1973**, Vol. *28,* p.769-781.

14. A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Pharm. Bull.*, **1978**, *26*, 2550.

15. W. J. Scott, G. T. Crips, and J. K. Stille, *J. Am. Chem. Soc.*, **1984**, *106*, 4630.

16. J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, **1986**, *25*, 508.

17. K. Sonogashira, Y. Tohda, and N. Hagihira, *Tetrahedron Lett.*, **1975**, 4467.

18. K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **1980**, *28*, 3488.

19. H. Yamanaka, M. Schiraiwa, K. Edo, and T. Sakamoto, *Chem. Pharm. Bull.*, **1979**, *27*, 270.

20. K. Tanzi, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **1982**, *30*, 1865.

21. S. Konno, M. Sagi, F. Siga, and H. Yamanaka, *Heterocycles,* **1992**, *34*, 225.

22. A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Pharm. Bull.*, **1980**, *28*, 3488.

23. I. N. Houpis, *Tetrahedron Lett.*, **1991**, *32*, 6675.

24. V. Farina, S. R. Baker, D. A. Benigni, S. I. Haude, and C. Jr. Sapino, *J. Org. Chem.*, **1990**, *55*, 5833.

25. T. A. Rano, M. L. Greenlee, and F.P. Dininno, *Tetrahedron Lett.*, **1990**, *31*, 2853.

26. G. K. Cook, W. J. Hornback, C. L. Jordan, J. H ; III, McDonald, and J. E. Munroe, *J. Org. Chem.*, **1989**, *54*, 5828.

27. G. T. Crips and S. Papadopoulos, *Aust. J. Chem.*, **1989**, 42, 279.

28. J. Sandosham, K. Undheim, and F. Rise, *Heterocycles,* **1993**, *35*, 235.

29. W. G. Gribble and S. C. Conway, *Synth. Commun.*, **1992**, *22*, 2129.

30. J. M. Fu and V. Snieckus, *Tetrahedron Lett.*, **1990**, *31*, 1665.

31. P. G. Ciattini, E. Moreva, and G. Ortar, *Tetrahedron Lett.*, **1992**, *33*, 4815.

32. Q. Zheng, Y. Yang, and A. R. Martin, *Tetrahedron Lett.*, **1993**, *34*, 2235.

33. R. F. Heck, In *Palladium Reagents in Organic Syntheses, ed. by A. R. Katritzky, O. MethCohn and C. W. Rees, Academic Press* **1985.**

34. J. Stang and T. E. Dueber, *Org. Synth., Coll. Vol., VI* **1988**, 757.

35. J. Suffert, *J. Org. Chem.*, **1989**, *52*, 509.

36. E. J. Corey, *J. Am. Chem. Soc.*, **1972**, *94*, 6190.

37. E. Ponnusamy, U. Fotadar, A. Spisni, and A. Fiat, *Synthesis*, **1986**, 48.

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