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A NEW FACILE SYNTHESIS OF 5-ARYL-4-TRIFLUOROACETYL-6-TRIFLUOROMETHYL-3,4-DIHYDRO-2*H*-1,3,4-OXADIAZINES FROM ARYLALDEHYDES

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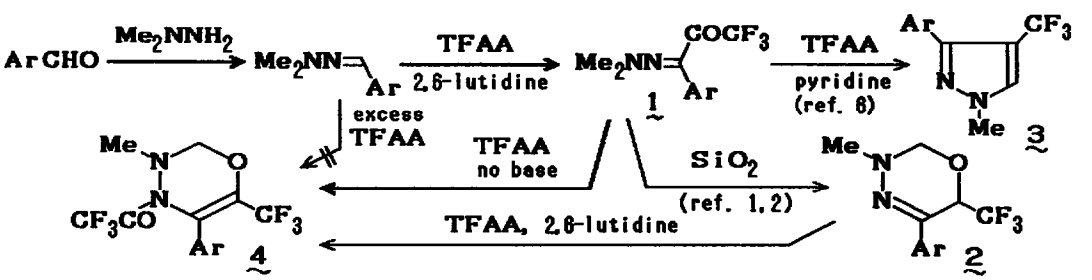
Summary: By reaction with an excess of trifluoroacetic anhydride, title compounds 4 were synthesized from C-trifluoroacetylated hydrazones 1 which are readily obtainable by trifluoroacetylation of arylaldehyde dimethylhydrazones.

Oxadiazine derivatives have attracted much attention of organic chemists from interests in their biological activities.[1,2,3] Recently we reported synthesis of 5-aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines (2) from C-trifluoroacetylated arylaldehyde dialkylhydrazones 1 using silica gel as an effective catalyst.[4,5] Later, we found that 1 treated with a large excess of trifluoroacetic anhydride (TFAA) in the presence of pyridine afforded 4-trifluoromethylpyrazoles (3) in good yields.[6] Interestingly, when this reaction is performed in the absence of pyridine, quite different reaction takes place to give 5-aryl-4-trifluoroacetyl-6-trifluoromethyl-3,4-dihydro-2*H*-1,3,4-oxadiazines (4), skeletal isomers of 2, in fair yields. This is a convenient three-steps synthesis of 4 from parent arylaldehydes. We now wish to communicate the results.



Hydrazones 1a-e were prepared by trifluoroacetylation of arylaldehyde dimethylhydrazones according to the manner reported previously.[4] For the reaction of 1 and TFAA, typical procedure is shown as follows. To an ice-cold solution of 1b (258 mg, 1 mmol) in anhyd. $CHCl_3$ (0.5 ml) was added dropwise TFAA (1.2 ml, 8.5 mmol) with continuous stirring. After stirring for 2 days at ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed thoroughly with 1N Na_2CO_3 solution (50 ml). The organic layer was dried over anhyd. $MgSO_4$ and the solvent was removed. The residual brown oil was purified by Kugelrohr distillation to afford 252 mg (71%) of 4b[7] as pale yellow oil. Quite similarly 4a and 4c-e could be obtained in moderate to good yields (see Table).

Compound 4 could not be obtained directly from arylaldehyde dimethylhydrazones by

Table Yields and ^{1}H NMR Spectral Data for 4a - e.

	Ar	time day	yield[a] %	oven temp.[b] °C/ torr	^{1}H NMR δ, ppm
4a	C_6H_5	2	46	135/3 (mp. 79.5°C)	7.25 (s, 5H, Ar), 4.91 (s, 2H, CH_2), 2.90 (s, 3H, NCH_3)
4b	*p*-$CH_3C_6H_4$	2	71	140/1	7.03 (s, 4H, Ar), 4.87 (s, 2H, CH_2), 2.87 (s, 3H, NCH_3), 2.31 (s, 3H, CH_3)
4c	*p*-$CH_3OC_6H_4$	8[c]	76	oil[d]	7.10, 6.76 (d, 2H, Ar), 4.89 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 2.90 (s, 3H, NCH_3)
4d	*p*-ClC_6H_4	4	39	105/1	6.97-7.33 (q, 4H, Ar), 4.92 (s, 2H, CH_2), 2.91 (s, 3H, NCH_3)
4e	*p*-$O_2NC_6H_4$	20[c]	43	oil[d]	8.10, 7.28 (d, 2H, Ar), 4.96 (s, 2H, CH_2), 2.94 (s, 3H, NCH_3)

[a] Isolated yield. [b] Kugelrohr distillation. [c] Reaction was carried out at 8°C. [d] These compounds were purified by silica gel column chromatography (ether/*n*-pentane= 3/7).

treatment with an excess of TFAA. Trifluoroacetylation of 2 (Ar= *p*-Tol) successfully proceeded to afford 4b in 75% yield when 2 (Ar= *p*-Tol) was treated with 8.5 mole equiv. of TFAA in the presence of 3 mole equiv. of 2,6-lutidine. However, in the absence of 2,6-lutidine, *i.e.*, the conditions from 1 to 4 shown in the Table, 2 afforded 4 in very low yields together with much unidentified materials. This suggests that the reaction from 1 to 4 does not proceed *via* 2 as an intermediate.

Detailed mechanistic studies and pharmacological activity tests for these newly synthesized oxadiazines, 4a-e are now in progress.

References and Notes

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7) 4b: IR (KBr) 1734(s), 1340(s), 1193(s), 1100(s) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 156.0(CO, $^2J_{CF}$= 36Hz), 132.0(C-6, $^2J_{CF}$= 37Hz), 119.9(CF_3, $^1J_{CF}$= 274Hz), 118.8(C-5), 115.8(CF_3CO, $^1J_{CF}$= 287Hz), 84.6(C-2, $^1J_{CH}$= 167Hz), 39.4(NCH_3), 139.3, 129.0, 127.6(Ar), 21.4 (CH_3). Anal. Calcd for $C_{14}H_{12}F_6N_2O_2$: C, 47.47; H, 3.41; N, 7.91; F, 32.18. Found C, 47.69; H, 3.59; N, 7.93; F, 32.08.

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