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PRELIMINARY NOTE

Thermal Conversion of Fluorinated Azo-compounds into Indazoles : the Case of 2,5,6-Trifluoro-4-(2,4,6-trimethylphenylazo)pyrimidine

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SUMMARY

Thermal dehydrofluorination of 2,5,6-trifluoro-4-(2,4,6-trimethylphenylazo)pyrimidine in boiling xylene to 2,4-difluoro-7,9-dimethyl-5H-pyrimido[4,5-c]benzo[1,2]diazepine is accompanied by the formation, inter alia, of 5,7-dimethyl-2-(2,5,6-trifluoropyrimidin-4-yl)-2H-indazole. The same product is formed when tetrafluoropyrimidine is treated with 5,7-dimethylindazole.

As pointed out previously [1], 2,5,6-trifluoro-4-(2,4,6-trimethylphenylazo)pyrimidine (**1**) does not undergo clean thermal solution-phase intramolecular dehydrofluorination to 2,4-difluoro-7,9-dimethyl-5H-pyrimido[4,5-c]benzo[1,2]diazepine (**2**), a situation which contrasts notably with the conversions (**3**) → (**4**) (>80% yield**; achieved in boiling mesitylene or 1,2-dichlorobenzene) and (**5**) → (**6**) (>95%; boiling xylene). We can now report that when a solution of the pyrimidinic azo-compound in 'mixed' xylenes (b.p. 138 °C) is heated under reflux for 2

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** Unless stated otherwise, all yields quoted here refer to isolated materials with correct elemental compositions (% by wt.).

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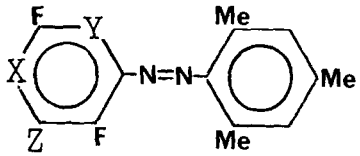
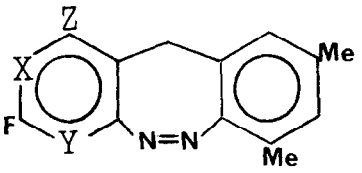


(1) X = Y = N, Z = F



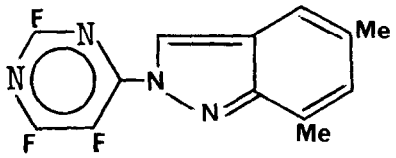
(2) X = Y = N, Z = F

(3) X = N, Y = CF, Z = F

(4) X = N, Y = CF, Z = F

(5) X = CF, Y = N, Z = $CF(CF_3)_2$

(6) X = CF, Y = N, Z = $CF(CF_3)_2$



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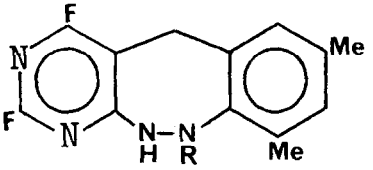
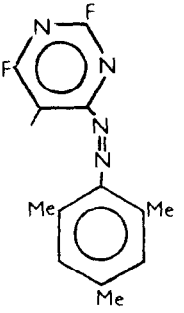
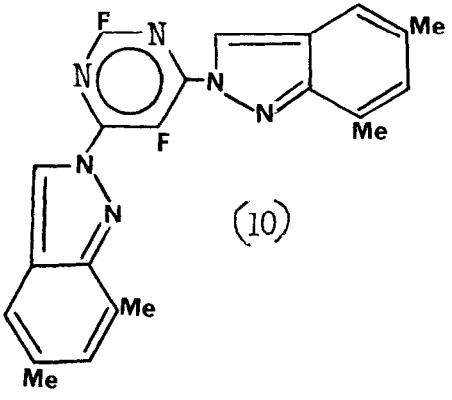


(8) R = H

(9) R =

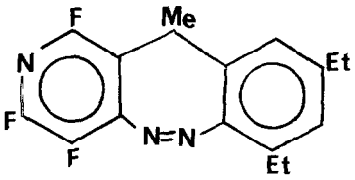




(10)

hours, almost complete (96%) conversion occurs to a mixture of 5,7-dimethyl-2-(2,5,6-trifluoropyrimidin-4-yl)-2H-indazole (**7**; 23%), the expected 1,2-diazepine (**2**; 21%), 2,4-difluoro-10,11-dihydro-7,9-dimethyl-5H-pyrimido[4,5-c]benzo[1,2]diazepine (**8**; 18%), and a red product (**9**; 4%) derived from nucleophilic attack on the starting material (**1**) by the last product (**8**). Each of these products was characterized by elemental analysis (C, H and N) and spectroscopic methods [i.r., n.m.r. (^{1}H, ^{19}F), and mass]; additionally, the dihydrodiazepine (**8**) was oxidised to the parent diazepine (**2**) with mercuric oxide and with tetrabutylammonium permanganate, and cleavage of the indazole (**7**) with hot ethanolic sodium ethoxide was shown to give 2,4,6-triethoxy-5-fluoropyrimidine (crude yield, 51%) and 5,7-dimethylindazole (62%). Identification of the indolizinic product from the thermal reorganization of the azo-compound (**1**) as the 2H- rather than the 1H-isomer rests on the precedent established by Elguero's group that phenylation of 7-methylindazole with 2,4-dinitrofluorobenzene occurs only at the 2- position, a result ascribed to steric hindrance [3]: treatment of tetrafluoropyrimidine with 5,7-dimethylindazole in boiling THF gave a compound identical with that formed from (**1**), together with a compound logically assigned the bis-indazole structure (**10**).

Discussion of the mechanism of the conversion (**1**) → (**7**) is deferred to a full presentation of the above work. Note, however, (i) that the pyrimidinylindazole (**7**) is stable in boiling xylene for a period (2 hours) equal to that employed in the original thermal reorganisation of azo-compound (**1**), i.e. the conversion (**7**) → (**2**) appears to be ruled out; (ii) no indolizinic products have been encountered in the several other reactions where production of 1,2-diazepines hinges on the presence of an ortho-methyl substituent in the starting azo-compound [1,2]; (iii) a mixture of a pyridobenzo-1,2-diazepine (**11**; 23%) and a pyridylindazole [assumed to be the 2H-isomer (**12**) (63%)] is obtained when the triethylated azo-compound 4-(2,4,6-$Et_3C_6H_2N{=}N$)C_5F_4N is heated in boiling 1,2-dichlorobenzene [2], a result which contrasts markedly with the 'clean' conversion (**3**) → (**4**) [1] referred to earlier; (iv) thermal formation of indazoles from unsymmetrical azo-arenes containing an ortho-methyl substituent in one ring but no recognizable nucleofuge in the other has been noted previously, e.g. the conversion (**13**) → (**14**) (93%) proceeds smoothly in boiling ethanol containing sodium carbonate and nitrosobenzene [4]; and (v) 5,7-dimethyl-2-(2,5,6-trifluoropyrimidin-4-yl)-2H-indazole (**7**) is formed, together with several as yet unidentified products but none of the possible pyrimidino-diazepine (**2**), when a solution of the



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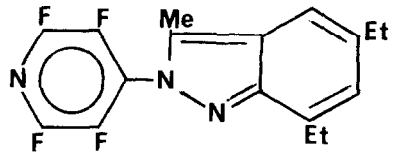

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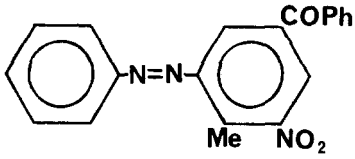

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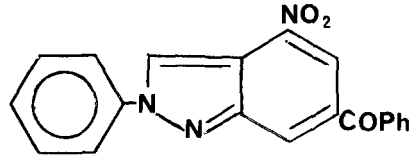

(14)

(phenylazo)pyrimidine (**1**) in toluene is boiled (111 °C) for 8 hours or kept for a long period in the dark at room temperature (**7** is easily detected by ^{19}F n.m.r. after 91 days).

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