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Fluoro Organics: A Facile and Exclusive Synthesis of Novel 2- or 4-Trifluoromethyl(1H,5)Arylodiazepines+

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Abstract: *Exclusive formation of either 2- or 4-trifluoromethyl(1H,5)arylodiazepines 4/3 was observed in the condensation of 1,1,1-trifluoro-3-(isobutoxymethylene)-2-propanones (R=H,COCF$_3$) 2 with o-arylenediamines 1 under microwave irradiation conditions. Thermal reactions under the same temperature and time produced no products.*

Arylodiazepines belong to an important class of compounds possessing a wide variety of medicinal properties.[1] Introduction of a trifluoromethyl group in the diazepine segment of the arylodiazepines is expected to enhance their anxiolytic activity and improve their pharmacological properties. In connection with a program aimed at evaluating this enhanced bioactivity, we have studied the synthesis of novel trifluoromethyl substituted (1H,5)arylodiazepines. The synthons **2a** and **2b** were selected for this purpose and prepared by reported procedures.[2,3] Condensation of the synthons with o-arylenediamines **1** in refluxing xylene led to a complex mixture of products unsuitable for preparative work.

Following examples of organic synthesis under microwave irradiation,[4,5] we examined the condensation of **1** with **2** in xylene under microwave irradiation. We report that it is a neat reaction producing a single product, either **3** or **4** in good yield (Scheme 1 and Table). A similar study[6] on the synthesis of 1,5-arylodiazepin-2-ones under microwave irradiation reports on having obtained mixtures of two isomeric arylodiazepinones with dissymetrical o-arylenediamines. In our work, products **3a-h,** 4-trifluoromethyl(1H,5)arylodiazepines were exclusively formed from o-arylenediamines **1a-d.** Products **4a-d,** 2-trifluoromethyl(1H,5)arlyodiazepines were formed from o-arylenediamines **1e** and **1f.** A successful extension of this facile condensation reaction is depicted in Scheme-2 with an aliphatic

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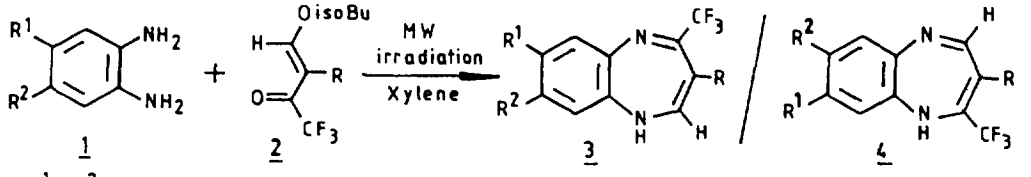
diamine **5** which gave exclusively **6**, the 4-trifluoromethyl diazepine product, without any admixture with the 2-trifluoromethyl isomer.

Typical procedure and product isolation: The experimental procedure consists in using a 50 ml Erlenmeyer flask containing o-xylene (10 ml), 15 mmoles of **2** and 15 mmoles of o-diamine. The mixture is then activated by microwave irradiation (980 w. multimode reactor) for a specified time . The mixture is cooled, concentrated by partially removing the solvent and passed through a column of silica gel, using hexane-chloroform mixture (1:4) as the eluant, to give crystalline compounds **3 / 4** in good purity.



1

a $R^1 = R^2 = H$
b $R^1 = R^2 = CH_3$
c $R^1 = H$, $R^2 = Cl$
d $R^1 = H$, $R^2 = CH_3$
e $R^1 = H$, $R^2 = -NO_2$
f $R^1 = H$, $R^2 = -COPh$

2

a R = H
b $R = -COCF_3$

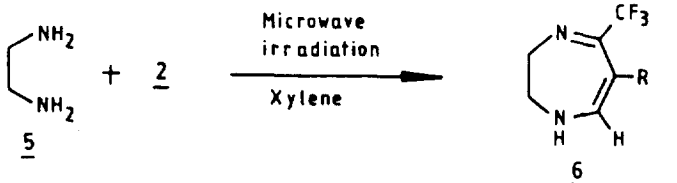
3

a $R = R^1 = R^2 = H$
b $R = H$, $R^1 = R^2 = CH_3$
c $R = R^1 = H$, $R^2 = Cl$
d $R = R^1 = H$, $R^2 = CH_3$
e $R = -COCF_3$, $R^1 = R^2 = H$
f $R = -COCF_3$, $R^1 = R^2 = CH_3$
g $R = -COCF_3$, $R^1 = H$, $R^2 = Cl$
h $R = -COCF_3$, $R^1 = H$, $R^2 = CH_3$

4

a $R = R^1 = H$, $R^2 = -NO_2$
b $R = R^1 = H$, $R^2 = -COPh$
c $R = -COCF_3$, $R^1 = H$
$R^2 = -NO_2$
d $R = -COCF_3$, $R^1 = H$
$R^2 = -COPh$

Scheme - 1



5

6

a R = H
b $R = -COCF_3$

Scheme - 2

Structures **3** and **4** of the products were established on the basis of spectroscopic data and the mode of formation. Since only either one of them is formed exclusively, the diagnostic features of ^1H NMR spectra[7] were useful in differentiating between the two isomeric structures. The spectra of **3** show the following characteristics: when R=H, a hump for NH (exchangeable in D_2O),a doublet of doublet for H-C(2) (reducing to a doublet with D_2O exchange) and a doublet for H-C(3); when R=-$COCF_3$, the signal for H-C(2) was a doublet changing into singlet on D_2O exchange.Similarly in the spectra of **4**, when R=H, H-C(3) and H-C(4) appeared as two doublets unaffected by D_2O exchange and when R=-$COCF_3$, H-C(4) gave rise to a singlet signal unaffected by D_2O exchange. Thus the relative positions of the protons and the trifluoromethyl groups were determined in the diazepine part of the molecule. Structure of product **6** was deduced on the basis of similar spectroscopic considerations.

TABLE

Entry#	Reaction Time in minutes	Yield %
3a	15	85
3b	20	93
3c	20	86
3d	20	80
3e	10	76
3f	15	84
3g	16	74
3h	18	83
4a	20	73
4b	20	75
4c	25	78
4d	22	80
6a	15	77
6b	12	73

#All compounds gave satisfactory analysis and found to possess one molecule of water of crystallisation.

The placement of substituents in the benzene segment was made on the basis of the mode of formation which may be formulated by counting upon the relative reactivities of the amino groups in the particular o-arylenediamine to initiate the reaction by displacing the isobutoxy group and to cyclise onto the carbonyl. Though the reaction course is same in all cases, the structure of the final stable product is determined by the influence of the trifluoromethyl as well as the nitro and the benzoyl groups. Thus, the presence of the trifluoromethyl group in the diazepine seems to stabilise structure **3** (as obtained from 1a to 1d) and structure **6**. Contrastingly, the effect of NO_2 or COPh is to stabilise structure **4**, despite interaction with the effect of the trifluoromethyl group. The remarkable feature about the products is that there is no prototropic shift from 1H to 5H. The products are stable and their chemistry is being studied.

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7. ^{1}H-NMR Spectral data for compounds ($CDCl_3$) in ppm.

   3b-δ 11.80 (br.,s,1H,NH); 7.60 (dd,J=6.6, 6.6 Hz ,1H,H-C(2)); 6.80 (s,1H,ArH); 6.60 (s,1H,ArH); 5.60 (d,J=6.6 Hz,1H,H-C(3)); 2.20 (s,6H,$2CH_3$).

   3f-δ 12.30 (s,br.,1H,NH); 8.35 (d,J=12.9 Hz,1H,H-C(2)); 6.90 (s,1H,ArH); 6.70 (s,1H,ArH); 2.20 (s,6H,$2CH_3$).

   4a-δ 11.40 (d,br.,1H,NH); 8.00 (d,J=12.1 Hz,1H,H-C(4)); 6.60 -7.80 (m,3H,ArH); 5.70 (d,J=9.0 Hz,1H,H-C(3)).

   4c-δ 11.10 (d,br.,1H,NH); 8.40 (s,1H,H-C(4)); 7.00-7.80 (m,3H,ArH).

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