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1,1,1,-TRICHLORO-3-[5-(2,4,6-TRIFLUOROPYRIMIDYL)]-3,4-EPOXYBUTANE

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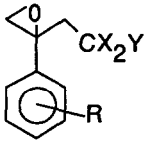
SUMMARY

The synthesis of 1,1,1-trichloro-3-[5-(2,4,6-trifluoropyrimidyl)]-3,4-epoxybutane has been accomplished in nine steps from diethyl malonate and urea The epoxide was prepared from the olefinic precursor via oxidation with anhydrous trifluoroperacetic acid in a non-buffered system Product isolation from trifluoroacetic acid solution demonstrates an unexpected stability of this class of epoxides toward protonic media

INTRODUCTION

Reports of significant herbicidal activity for a number of aryl substituted epoxy alkanes, 1, have generated an interest in their synthesis [1] The effect of structural



1

X = halogen
Y = X or CF_3
R = X, Y, alkyl etc

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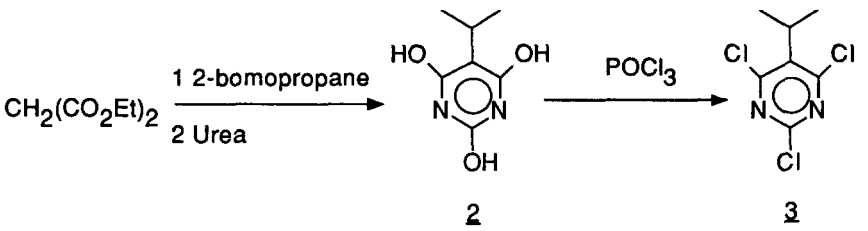
modifications of X, Y and R on the herbicidal activity has been extensively investigated However substitution of a heterocyclic ring for the benzene ring has received little attention Herein, we describe the synthesis of a pyrimidine member of this class of herbicides

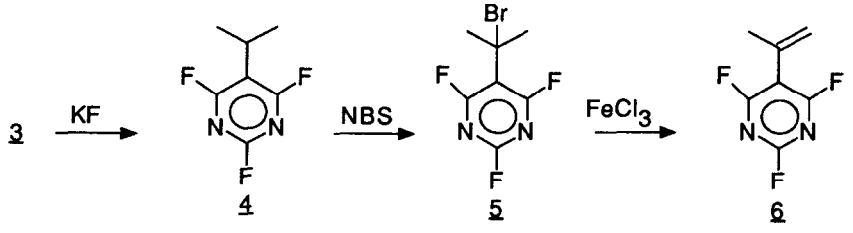
RESULTS AND DISCUSSION

The classical barbituric acid model was selected for construction of the pyrimidine ring [2] Akylation of diethyl malonate with 2-bromopropane in sodium methoxide-methanol gave isopropyl diethyl malonate The latter was not isolated but condensed with urea in the same reaction vessel to give 2,4,6-trihydroxy-5-isopropyl pyrimidine 2 Phosphorous oxychloride converted 2 to the desired trichloro



2 3

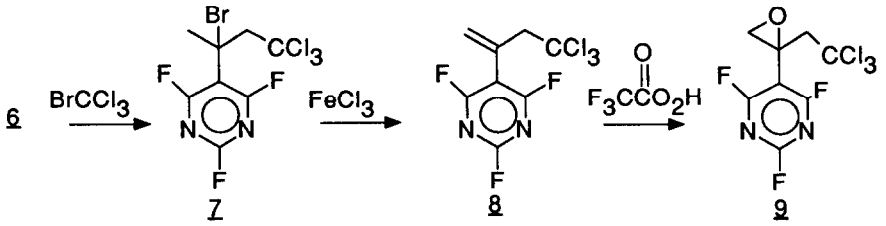
derivative 3 which undergoes a facile halogen exchange with anhydrous potassium fluoride to give the desired 2,4,6-trifluoro-5-isopropylpyrimidine 4 Functionalization of the isopropyl side chain via benzylic halogenation with N-bromosuccinimide



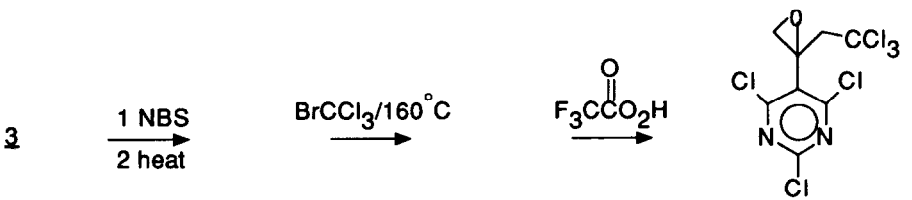
4 5 6

under ultraviolet radiation gave 5 The latter was readily dehydrohalogenated in the presence of ferric chloride to the isopropenyl derivative 6 which is the desired intermediate for elaboration of the side chain

In previous work, the transition metal catalyzed addition of polyhalogens to olefins has been utilized to extend the carbon side chain For example, the addition of carbon tetrachloride, catalyzed by CuCl, has been carried out to give derivatives of 1 (X =Y =Cl) Olefin 6 reacted smoothly with the more active polyhalogen bromotrichloromethane without a catalyst to give 7 which dehydrohalogenated in the presence of ferric chloride to give olefin 8 The final step of the reaction sequence



the oxidation of 8, was carried out at room temperature with trifluoroperacetic acid solution without added buffer Previously reported epoxidation of olefins with trifluoroperacetic acid required the presence of buffers, preferably solid sodium bicarbonate, to prevent formation of hydroxy trifluoracetates [3] The stability of 9 toward the byproduct trifluoroacetic acid is presumably due to steric and electronic factors [4] This is supported by the synthesis of 10 The trichloro derivative 3 was converted to 10 via the same reaction sequence as that described above The trichloro derivatives eliminate hydrogen bromide more readily than do the trifluoro analogs, whereas the trifluoro derivative undergoes bromination and addition of bromotrichloromethane more rapidly than does the trichloro derivative Thus steric factors appear to be controlling the side chain reactivity The trichloro derivative inhibits addition because of steric compression and facilitates elimination because of steric relief



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EXPERIMENTAL

General Comments

All melting points were taken in capillary tubes in air with a Thomas-Hoover Uni-melt apparatus and are uncorrected ^{1}H and ^{13}C NMR spectra were recorded on either an IBM-Bruker NR-80 (80 066 MHz and 20 11 MHz respectively) or Varian XL-300 (299 916 MHz and 75 42 MHz respectively) spectrometer using DMSO-d6 as solvent except where noted with solvent peak as standard NMR spectra are reported in the following fomat δ (multiplicity, assignment coupling constant number of hydrogens [^{1}H only]) Mass spectra were recorded on a Hewlett-Packard 5995 and are reported as amu (assignment relative intensity) where possible HPLC analysis was performed on a Hewlett-Packard 1090-HPLC equipped with a Brownlee guard column (30 X 2 1 mm 51 RP-8 Sphere) and Shandon analytical column (100 X 2 1 mm 5mm Hypersil) Analysis method was 15% acetonitrile/water hold for 1 minute at 0 6 mL/min then ramp to 90% acetonitrile/water at 3 minutes (water contained 0 1 wt% acetic acid) UV detection was used at 232 nm Gas chromatography was performed on a Hewlett-Packard 5710A GC with OV-17 packed column using thermal conductivity detection and temperature gradient 100-280°C at 16°C/min

Isopropyl diethyl malonate

2-Bromopropane (188 mL 2 mol) was added dropwise to a refluxing solution of diethyl malonate (320 mL 2 mol) and sodium ethoxide (980 mL 21% solution 2 5 mol) The mixture was stirred for 8-10 hours The product was not isolated but used directly in the next reaction A small portion of the product mixture was analyzed ^{1}H NMR ($CDCl_3$) 1 0 (d, $(CH_3)_2CH$, J=6 Hz, 6H) 1 3 (t, OCH_2CH_3, J=8 Hz 6H) 2 4 (d septet, $(CH_3)_2CHCH$-, J=6 Hz, 2 Hz 1H) 3 1 (d, $(CH_3)_2CHCH$-, J=6 Hz, 1H), 4 2 (q OCH_2CH_3 J=8 Hz 4H) b p 75-78°C (0 2 mm)

2,4,6-Trihydroxy-5-isopropylpyrimidine 2 (nc)

To the above reaction mixture was added sodium pieces (46 g, 2 mol) and urea (112 g, 2 mol) dissolved in methanol The entire reaction was carried out under nitrogen The mixture was refluxed overnight The mixture diluted with 1 liter HOT WATER and 70 mL conc HCl The cooled reaction mixture was filtered, the filter cake washed and dried to afford the product as a white crystalline solid 230 g (~ 70%) m p 208-210°C

2,4,6-Trichloro-5-isopropylpyrimidine 3 (nc)

Phosphorous oxychloride (200 mL) was added dropwise to a stirred mixture of 2,4,6-trihydroxy-5-isopropylpyrimidine (170 g, 1 mol) and 2,6-lutidine (800 mL) with external cooling After the addition was complete, the mixture was refluxed overnight The cooled mixture was concentrated under reduced pressure and this viscous concentrate poured carefully onto crushed ice with vigorous stirring The cold, dark mixture was extracted with methylene chloride, the organic layer washed, dried, concentrated and distilled to give 3 as a low melting, white solid 200 g (89%) m p 67-71°C, M S 228 ($m^+ + 4$, 8), 226 ($m^+ + 2$, 19), 224 (m^+, 22), 211 [($m^+ + 2$)-CH_3, 100], 209 (m^+ -CH_3,85) 173 (m^+ -CH_4Cl, 34)

2,4,6-Trifluoro-5-isopropylpyrimidine 4 (nc)

3 (27 g, 0 12 mol), anhydrous potassium fluoride (25 g, 0 43 mol) and 18-Crown-6 (1 g, catalytic) were stirred in acetonitrile (400 mL, anhydrous) at 40°C overnight under nitrogen The mixture was poured into water and extracted with methylene chloride The organic layer was dried, carefully concentrated in vacuo without heating and the concentrate distilled to give 4 as a clear liquid 21 g (99%), b p 121-122°C M S 176 (m^+ 14), 161 (m^+ -CH_3, 100)

2 [5 (2,4,6 Trifluoropyrimidyl)] 2 bromopropane 5 (nc)

4 (42 g, 0 24 mol) and N-bromosuccinimide (45 g 0 25 mol) were refluxed in CCl_4 (400 mL) under a U V lamp in a quartz three-necked round bottom flask, the reaction requiring 4-6 hours The cooled mixture was filtered, the filtrate washed in cool 5N NaOH dried and concentrated in vacuo A small portion of the crude concentrate was analyzed and shown to be 5 ^{1}H NMR ($CDCl_3$) 2 30 (t, -CH_3,J =2 4 Hz) M S 255 (m^+ +1 21), 253 (m^+ -1 20) 174 (m^+ -HBr,31), 147 (m^+ -C_2H_4 Br, 100)

2,4,6-Trifluoro-5-(2-propenyl)-pyrimidine 6

Reaction concentrate from 5 was distilled with catalytic $FeCl_3$ at atmospheric pressure to give 6 as a clear liquid in near quantitative yield from 5 b p 146-147 5°C, ^{1}H NMR ($CDCl_3$) 2 1 (s(br) CH_3, 3H) 5 25 (s(br), =CH_2 a or B 1H), 5 55 (s(br), =CH_2 a or B, 1H), M S 174 (m^+,83) 147 (m^+ -C_2H_3, 100)

1,1,1-Trichloro-3-[5-(2,4,6-trifluoropyrimidyl)-3-bromobutane 7 (nc)

6 (40 g 0 23 mol) was stirred in bromotrichloromethane (200 mL) under a U V lamp in a quartz three-necked round bottom flask for 30 minutes the reaction temperature approaching reflux The solution was concentrated in vacuo and a small portion of the crude concentrate analyzed and shown to be 7 M S 293 [(m^+ +4)-Br, 2], 291 [(m^+ + 2)-Br, 2], 240 (m^+ -CH_2BrCl 10), 194 (m^+ -CH_2BrCl_2, 100)

1,1,1-Trichloro-3-[5-(2,4,6-trifluoropyrimidyl)]-but-3-ene 8 (nc)

The reaction concentrate from 7 was distilled over catalytic $FeCl_3$ at reduced pressure to afford 8 as a clear liquid 50 g (75% from 6), b p 68-71°C (1 mm), ^1H NMR ($CDCl_3$) 3 81 (s, CH_2CCl_3 2H), 5 76 (s(br) = CH_2 a or B 1H), 5 94 (s(br), = CH_2 a or B 1H) M S 292 (m^+ + 2 2), 290 (m^+ 2), 241 (m^+ CH_2Cl, 100)

1,1,1-Trichloro-3-[5-(2,4,6-trifluoropyrimidyl)]-3,4 epoxybutane 9 (nc)

To a 1 liter three necked round bottom flask containing 1,2-dichloroethane (300 mL) and 70% hydrogen peroxide (21 g, 0 43 mol) was added trifluoroacetic anhydride (104 mL 0 74 mol) slowly with cooling After 0 5 hr, olefin 8 (15 g 0 5 mol) was added dropwise in 1 2-dichloroethane (100mL) The reaction was conducted under a nitrogen purge at 30°C and required 36 hours to complete conversion A saturated sodium bisulfite solution was added and the layers separated The organic layer was washed with saturated sodium chloride solution water dried over anhydrous magnesium sulfate and concentrated The concentrate was distilled at reduced pressure to give 9 as a clear liquid in near quantitative yield b p 69-70°C (0 35mm) ^1H NMR ($CDCl_3$) 2 8-4 0 (complex multiple) M S 243 [(m^+ + 2) -CH_2OCl 5] 241 (m^+ -CH_2OCl, 9), 207 [(m^+ + 2)-CH_3OCl_2, 13], 205 (m^+ -CH_3OCl_2, 4), 161 (m^+ -C_2OCl_3 100)

2 [5-(2,4,6-Trichloropyrimidine)]-2 bromopropane (nc)

To a 250 mL three necked round bottom quartz flask was added 3 (11 22 g, 0 5 mol), N bromosuccinimide (8 9 g, 0 05 mol) and CCl_4 (100 mL) and the mixture refluxed under a general purpose U V lamp overnight The cooled mixture was filtered, the filtrate washed with cool 5N NaOH dried and concentrated to give the product as a white solid 11 2 g (75%), ^1H NMR ($CDCl_3$) 2 1 (s -CH_3), M S 304 (m^+ + 4, 8), 302 (m^+ + 2 9), 300 (m^+, 5), 225 [(m^+ + 4)-Br 23] 223 [(m^+ +2) Br, 68], 221 (m^+ -Br, 68) 188 [(m^+ + 2)-BrCl, 64], 186 (m^+ -BrCl, 100)

2,4,6-Trichloro-5-(2-propenyl)-pyrimidine (nc)

Distillation of the above bromide at (1mm) afforded olefin as a white solid in 80% yield, m p 45-47°C, ^{1}H NMR ($CDCl_3$) 2 1 (m, -CH_3, 3H), 5 1 (s(br), =CH_2 a or B, 1H), 5 5 (m = CH_2 a or B 1H) M S 224 (m^+ + 2 47) 222 (m^+ 46) 189 [(m^+ + 2)-Cl 25], 187 (m^+ -Cl, 43), 151 (m^+ -HCl_2, 49)

1,1,1-Trichloro-3-[5-(2,4,6-trichloropyrimidine)] but-3-ene (nc)

A 200 mL Parr bomb was charged with the above olefin (2 2 g, 0 01 mol) cuprous chloride (catalytic), 2,6-lutidine (I 5 g, I 6 mL 0 015 mol) and bromotrichloromethane (50 mL) and stirred at 160°C for 12-24 hours The cooled mixture was filtered, the filtrate washed with 1 N HCl (aq), water, dried, and concen trated The crude product was flash column chromatographed on silica to afford 1,1,1 trichloro 3 [5 (2,4,6 trichloropyrimidine)] but 3 ene as a white crystalline solid 0 8 g (25%) m p 110-111°C ^{1}H NMR ($CDCl_3$) 3 9 (s(br), -CH_3, 3H), 5 7 (s(br) = CH_2 a or B, 1H), 6 0 (m, = CH_2 a or B, 1H), M S 307 [(m + 4) -Cl, 5], 305 [m^+ + 2) -Cl 9], 303 (m^+ -Cl 6) 295 [(m^+ + 6)-CH_2Cl 21] 293 [(m^+ + 4) CH_2Cl 67], 291 [m^+ + 2) - CH_2Cl, 100], 289 (m^+ -CH_2Cl, 66)
Calcd for $C_8H_4N_2Cl_6$ C, 28 2, H, 1 18, N, 8 22, Cl, 62 4
Found C 28 3 H 1 37, N 8 12, Cl, 63

1,1,1-Trichloro-3-[5-(2,4,6-trichloropyrimidyl)]-3,4-epoxybutane 10 (nc)

To a 250 mL three necked round bottom flask containing 1 2-dichloroethane (100mL) and 70% hydrogen peroxide (0 2 g, 0 004 mol) was added trifluoroacetic anhydride (10 mL, 14 9 g, 0 07 mol) slowly with cooling After 30 minutes the above olefin (1 g, 0 003 mol) was added dropwise in 1,2-dichloroethane (20 mL) The entire reaction was conducted under a nitrogen purge at 30°C and required 36 hours to complete conversion A saturated sodium bisulfite solution was added, the layers separated, the organic layer washed with saturated NaCl solution water, dried and concentrated Product 10 is left after concentration in near analytical purity in a quantitative yield, m p 123-124°C ^{1}H NMR ($CDCl_3$) 3-4 (complex multiple) M S 325 [m^+ + 6)-Cl, 10], 323 [m^+ + 4)-Cl, 25], 321 [(m^+ + 4) CH_2OCl, 40], 291 [(m^+ +2) CH_2OCl 90], 289 (m^+ -CH_2OCl, 55)
Calcd for $C_8H_4N_2OCl_6$, C, 26 93, H, 1 13, N, 7 85
Found C, 26 9, H, 1 35, N, 7 74

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