Pergamon

Tetrahedron Letters 39 (1998) 8483–8486

TETRAHEDRON LETTERS

Studies on Quinazolines IX:[1] Fluorination versus 1,2-Migration in the Reaction of 1,3-Bifunctionalized amino-2-propanol with DAST

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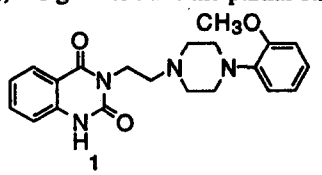
Received 23 April 1998; accepted 7 September 1998

Abstract: *Treatment of 1-phthaloylamino-3-[4-(2-methoxyphenyl)piperazin-1-yl]-propanol (7) with DAST induced 1,2-migration via a proposed spiro-aziridinium intermediate to give N-[2-fluoro-3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-phthalimide (11a) in 13 % yield and N-[2-fluoromethyl-2-[4-(2-methoxyphenyl)-piperazin-1-yl]ethyl]phthalimide (11b) in 73% yield.*

Compounds containing aryl piperazines constitute a class of important agents with a variety of pharmacological activities *via* acting as neurotransmitter blockers such as 5-hydroxytryptamine antagonists,[2] α_{1a}-adrenoceptor blockers[3] as well as opioid receptor σ binding site ligands.[4] SGB-1534 (1)[5] and pelanserin (2)[6] were recently reported to be an α_{1a}-blocker and a $5HT_2$ antagonist, respectively. Introduction of fluorine into biologically active organic substances is one of the most simple structural modifications used in order to increase their activity.[7] 3-[2-Fluoro-3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]quinazolin-2,4-(1*H*, 3*H*)-dione (**3a**), designed to have the partial structure of precedent compounds, is of special interest to us.



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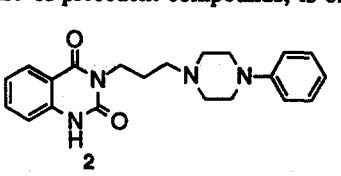

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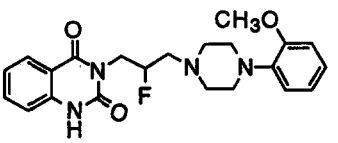
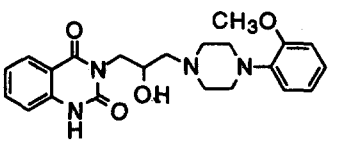


3a



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During the course of studies aimed at introducing a fluorine atom in place of the hydroxy group in 3-[2-hydroxy-3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]quinazolin-2,4-(1*H*, 3*H*)-dione (**4**) , the reaction of **4** with diethylaminosulfur trifluoride (DAST) was investigated. The preparation of **4** began with the reaction of glycidol (**5**) with phthalimide under Mitsunobu conditions, then treating *N*-(2,3-epoxypropyl)phthalimide (**6**) with 2-methoxyphenylpiperazine, subsequently removing the protecting group of 1-phthaloyl-amino-3-[4-(2-methoxyphenyl)piperazin-1-yl]propanol (**7**) by hydrazine monohydrate to give 1-amino-3-[4-(2-methoxyphenyl)piperazin-1-yl]propanol (**8**). Condensation of **8** with isatoic anhydride afforded 2-amino-*N*-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-2-ol]benzamide (**9**) in 92% yield which was then reacted with triphosgene furnishing **4** in 19% yield. However, when **4** was subjected to fluorination with DAST, 2-[4-(2-

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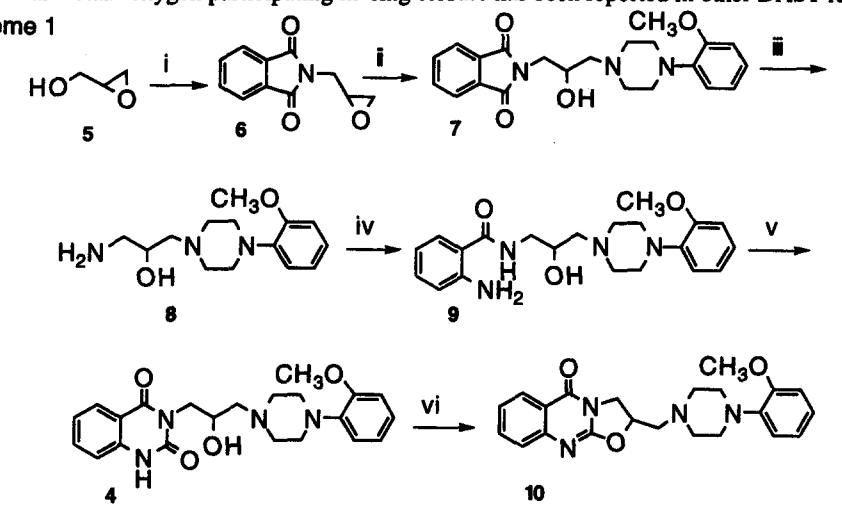
PII: S0040-4039(98)01905-4

methoxyphenyl)piperazin-1-yl]methyl[2,3-*b*]quinazolin-5-one (**10**) was obtained in 84% instead of **3a**. (Scheme 1) Similar lactam oxygen participating in ring closure has been reported in other DAST reactions. [8]

Scheme 1



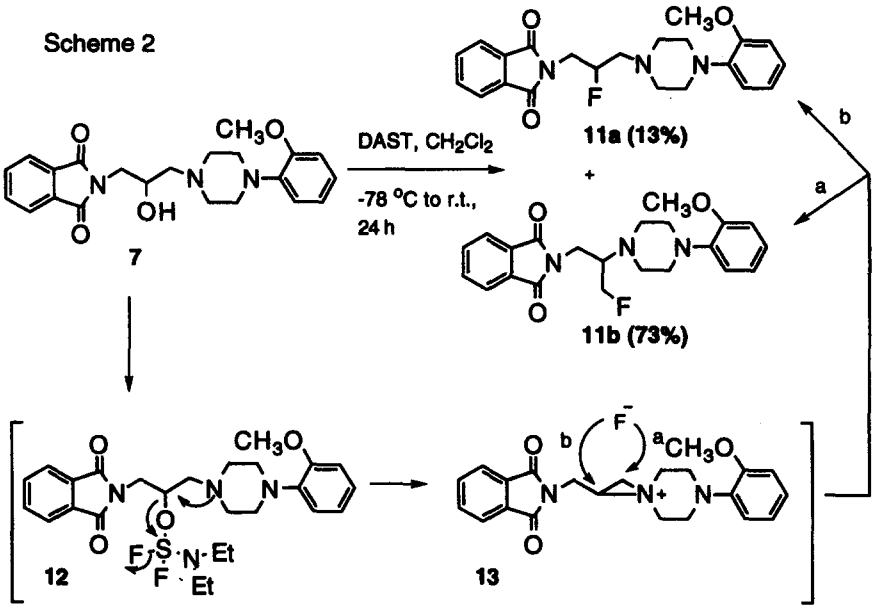
i, phthalimide, Ph_3P, DEAD, THF, r.t, 18 h, 72%; ii, 1-(2-methyoxyphenyl)piperazine, THF, reflux, 72 h, 64%; iii, hydrazine monohydrate, ethanol, 5 h, 92%; iv, isatoic anhydride, DMF, 45 °C, 1 h, 92%; v, triphosgene, Et_3N, 1,4-dioxane, r.t., 17 h, 19%; vi, DAST, CH_2Cl_2, -78 °C to r.t., 24 h, 84%.

To avoid the lactam oxygen anchimeric participation, we reasoned that treatment of **7** with DAST should provide *N*-[2-fluoro-3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]phthalimide (**11a**) which should be taken through the same pathway as Scheme 1 to obtain **3a**. Interestingly, when **7** was treated with DAST in dichloromethane at room temperature for 1 day, it gave only a 13 % yield of **11a**[9]. Another product was isolated and found to be *N*-[2-fluoromethyl-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]phthalimide (**11b**)[10] in 73% yield. The ^{13}C NMR spectrum of **11b** revealed that there is one doublet centered at δ 35.85 with a coupling constant of 8.0 Hz, indicative of the assigned carbon and fluorine atom separated by two carbon atoms.[11] This reaction might proceed via an initial nucleophilic attack of the hydroxy group on the DAST to form intermediate **12** which is followed by intramolecular displacement of the C-2 leaving group through anchimeric participation of piperazine moiety to form the spiro aziridinium intermediate **13**. Subsequently, a ring opening of **13** by fluoride ion either through the less hindered carbon (pathway a) to give **11b** as major product or through the more hindered carbon (pathway b) to furnish **11a** would account to product formation. (Scheme 2) Alternatively, **11a** could be obtained by direct nucleophilic displacement of the C-2 leaving group by fluoride ion.

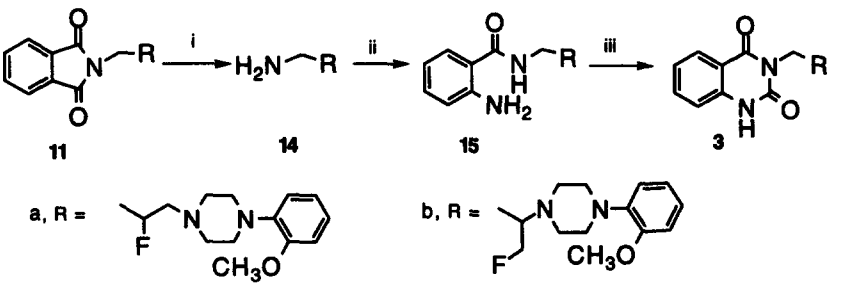
Compound **11a** was subjected to deprotection using hydrazine monohydrate, then a condensation of the resulting 2-fluoro-3-[4-(2-methoxyphenyl)piperazin-1-yl]propylamine (**14a**) with isatoic anhydride gave 2-amino-*N*-[2-fluoro-3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]benzamide (**15a**) which was subsequently condensed with triphosgene to furnish **3a**[12] in 62% yield. (Scheme 3) Similarly, 2-fluoromethyl-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethylamine (**14b**) that was obtained in 53% yield by a treatment of **11b** with hydrazine was condensed with isatoic anhydride to give 2-amino-*N*-[2-fluoromethyl-2-[4-(2-methoxyphenyl)-

piperazin-1-yl]ethyl]benzamide (**15b**) in 69% yield. A condensation of **15b** with triphosgene afforded 3-[2-fluoromethyl-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]quinazolin-2,4-(1*H*, 3*H*)-dione (**3b**)[13] in 95 % yield.

Scheme 2



Scheme 3



i, $N_2H_4.H_2O$, EtOH, reflux, 17 h, **14a** (86%), **14b** (53%); ii, isatoic anhydride, DMF, 45 °C, 5 h, **15a** (88%), **15b** (69%); iii, triphosgene, Et_3N, 1,4-dioxane, r.t., 12 h, **3a** (62%), **3b** (95%)

A perusal of the literature indicates that participation of neighboring groups induced migrations by DAST, such as, allylic or homoallylic rearrangements,[14] dehydration and/or 1,2-shifts,[15] ether formation,[16] epimerization,[17] norbornyl cation rearrangements[18] have previously been reported. However, to our best of knowledge, the 1,2-migration of 1,3-bifunctionalized amino-2-propanol into 1,2-bifunctionalized amino-1-fluoromethylethane by DAST has never been reported. Thus, this investigation provides a practical approach for the preparation of 1-fluoroethylamine derivatives. The biological and pharmacological profiles of **3a-b** and the synthesis of related compounds are under active investigation in this laboratory and the results of these studies will be reported elsewhere in the due course.

Acknowledgement: This investiagtion was supported by research grant from Nationa Science Council (No. NSC 86-2314-B-002-)88-M38) of the Republic of China. Drs.Cyril O. Usifoh and Alexander Gutsait are on leave from the University of Benin, Nigeria and Regina Technical University, Latvia.

References and Notes:

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9. Compound **11a**: m.p.141 ^{o}C ; MS *m/z* 397.2 (M^+) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H, ArH), 7.72-7.70 (m, 2H, ArH), 6.97-6.82 (m, 4H, ArH), 5.07-4.91 (m, 1H, CHF), 4.11-3.87 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.01 (br s, 4H, NCH_2), 2.79-2.66 (m, 6H, CH_2, NCH_2) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.11, 152.40, 141.51, 134.08, 132.04, 123.40, 122.88, 120.94, 118.14, 111.18, 88.72 (d, J = 173.4 Hz, CF), 60.02 (d, J = 21.1 Hz), 55.32, 54.04, 50.51, 40.44 (d, J = 24.2 Hz). Anal. Calcd for $C_{22}H_{24}O_3N_3F$: C, 66.50; H, 6.09; N, 10.60. Found: C, 66.28; H, 6.06; N, 10.47.
10. Compound **11b**: m.p.154 ^{o}C ; MS *m/z* 397.2 (M^+) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 3.1, 5.4 Hz, 2H, ArH), 7.70 (dd, J = 3.1, 5.4 Hz, 2H, ArH), 6.94-6.80 (m, 4H, ArH), 4.71 (dd, $J_{H,H}$ = 3.7, 4.9 Hz, $J_{F,H}$ = 47.3 Hz, 1H, CH_AHF), 4.59 (dd, $J_{H,H}$ = 3.7, 4.9 Hz; $J_{F,H}$ = 47.3 Hz, 1H, CHH_BF) , 4.06 (dd, J = 9.3, 14.0 Hz; $J_{F,H}$ = 144 Hz, 1H, CH_AH), 3.82 (s, 3H, OCH_3), 3.68 (dd, J = 6.1, 14.1 Hz,; $J_{F,H}$ = 144 Hz, 1H, CHH_B) , 3.33-3.23 (m, 1H, CH), 3.07-3.02 (m, 2H), 2.90 (m, 4H, NCH_2), 2.74-2.69 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.33, 152.43, 141.34, 133.89, 132.09, 123.20, 122.72, 120.82, 118.10, 111.11, 81.30 (d, J = 172.3 Hz, CF), 61.31 (d, J = 17.6 Hz), 55.28, 51.23, 49.39, 35.85 (d, J = 8.0 Hz). Anal. Calcd for $C_{22}H_{24}O_3N_3F$: C, 66.50; H, 6.09; N, 10.60. Found: C, 66.17; H, 6.10; N, 10.43.
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12. Compound **3a**: MS *m/z* 412.1 (M^+) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1H, NH), 8.12 (d, 1H, J = 7.68 Hz, ArH), 7.58 (t, 1H, J = 7.26 Hz, ArH), 7.23 (t, 1H, J = 7.56 Hz, ArH), 7.12 (d, 1H, J = 8.19 Hz, ArH), 7.02-6.99 (m, 1H, ArH), 6.92-6.85 (m, 3H, ArH), 5.30-5.10 (m, 1H, CHF), 4.67-4.56 (m, 1H, CH_2), 4.24 (ddd, 1H, J =24.39, 13.68, 3.72 Hz,CH_2), 3.86 (s, 3H, OCH_3), 3.11 (br s, 4H, NCH_2), 2.91-2.83 (m, 6H, NCH_2, CH_2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.07, 152.80, 152.62, 141.68, 139.18, 135.76, 128.98, 124.08, 123.58, 121.55, 118.78, 115.70, 115.00, 111.75, 89.48 (d, J = 172.88 Hz, CF), 60.71 (d, J = 21.25 Hz), 55.92, 54.54, 51.00, 43.53 (d, J = 24.16 Hz) ; Ana. Calcd for $C_{22}H_{25}O_3N_4F$ (412.46): C, 64.10 ; H, 6.11 ; N, 13.60 . Found: C, 63.70 ; H, 6.14 ; N, 13.40 .
13. Compound **3b**: m.p. 180-181 ^{o}C ; MS *m/z* 412 (M^+) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H, NH), 8.12 (dd, J = 1.3, 8.0 Hz, 1H, ArH), 7.59 (dt, J = 1.4, 7.7 Hz, 1H, ArH), 7.23 (dt, J = 0.8, 7.57 Hz, 1 Hz, 1H, ArH), 7.06 (d, J = 8.0 Hz, 1H, ArH), 6.93 (dt, J = 1.7, 7.6 Hz, 1H, ArH), 6.82-6.78 (m, 3H, ArH), 4.74-4.73 (m, 1H, CH, CH_AHF), 4.62-4.61 (m, 1H, CH, CHH_BF), 4.48 (dd, $J_{H,H}$ = 8.3, 13.1 Hz; $J_{F,H}$ = 158 Hz, 1H, CH_AH), 4.08 (dd, $J_{H,H}$ = 6.3, 13.6 Hz; $J_{F,H}$ = 158 Hz, CHH_B), 3.81 (s, 3H, OCH_3), 3.41-3.33 (m, 1H, CH), 3.11-3.08 (m, 2H), 2.94 (m, 4H, NCH_2), 2.80-2.77 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.05, 152.91, 152.72, 141.92, 139.20, 135.66, 128.96, 124.05, 123.32, 121.42, 118.64, 115.56, 115.11, 111.69, 82.34 (d, J = 171.74 Hz, CF), 62.04 (d, J = 17.96 Hz), 55.86, 51.86, 50.19, 39.05 (d, J = 8.35 Hz). Anal Calcd for $C_{22}H_{25}O_3N_4F \cdot 1/4H_2O$: C, 63.37 ; H, 6.16 ; N, 13.44 . Found: C, 63.49 ; H, 6.33 ; N, 12.37.
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