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A New Approach to Pyrrolo[1,2-a]quinoxaline Derivatives

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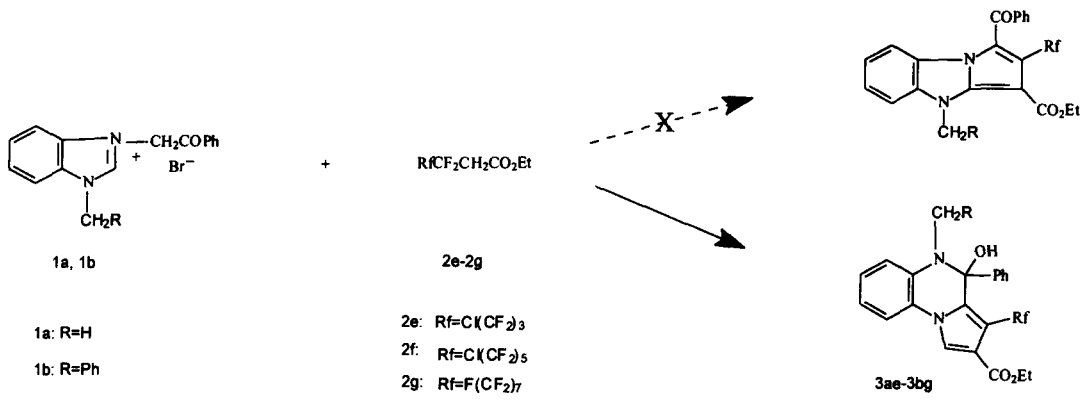
Abstract: In the presence of base , ethyl 2,2-dihydropoly(per)fluoroalkanoate(**2**) reacted with N-phenacyl benzimidazole bromide(**1a-1b**),N-acetonyl benzimidazole bromide(**1c**) and N-ethoxycarbonylmethyl benzimidazole bromide(**1d**) in DMF to give pyrrolo[1,2-a]quinoxaline derivatives(**3ae-3dg**) respectively. © 1997 Elsevier Science Ltd.

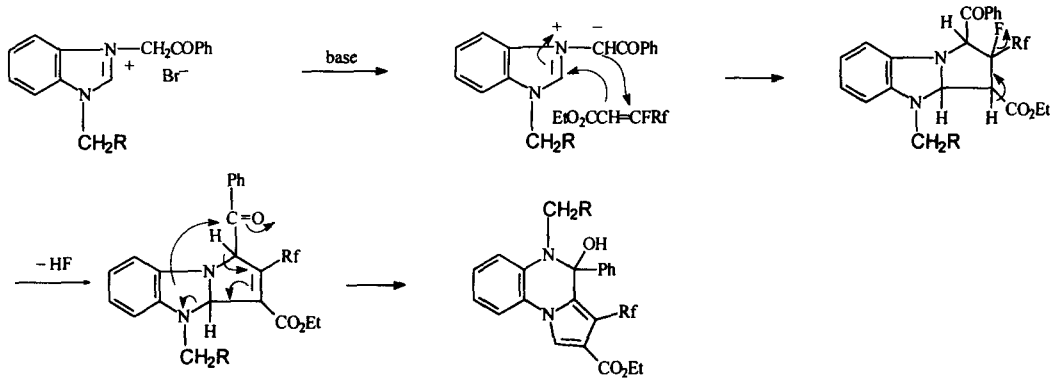
Tricyclic ring system pyrrolo[1,2-a]quinoxaline derivatives may be formed by the addition of a two carbon unit to 2-methylquinoxaline [1,2] , the intramolecular cyclization of a quinoxaline substituted three carbon side chain at position 2 [3] , the intermolecular cyclization of 2-hydroxy-1,5-diketone with o-phenylenediamine [4] and other methods [5-7] . In the present paper , we wish to provide a new approach to this tricyclic heterocyclic compounds.

Recently, we have reported the synthesis of F-alkyl substituted pyrazolo[1,2-a]pyridine , pyrrolo[1,2-b]pyridazine and indolizine derivatives from the corresponding N-ylides with ethyl 2,2-dihydropoly(per)fluoroalkanoates [8]. In a similar way ,we tried to synthesize 2-fluoroalkyl-substituted 4-H-pyrrolo[1,2-a]benzimidazole derivatives starting from N-phenacyl benzimidazole bromide and ethyl 2,2-dihydropoly(per)floroalkanoates . To our surprise , the only product isolated was not the expected 4-H-pyrrolo[1,2-a]benzimidazole derivative , the NMR, MS , IR spectra and elemental analysis of the product showed that a pyrrolo[1,2-a]quinoxaline derivative (**3**) was formed in the reaction .

When N-phenacyl benzimidazole bromide(**1a-1b**) was allowed to react with ethyl 2,2-dihydropoly(per)fluoroalkanoates (**2**) under basic condition , 3-fluoroalkyl-4-phenyl-4-hydroxyl-pyrrolo[1,2-a]quinoxaline derivatives (**3ae-3bg**) was obtained in high yield. The structure of **3ae** was confirmed by X-ray crystallography.

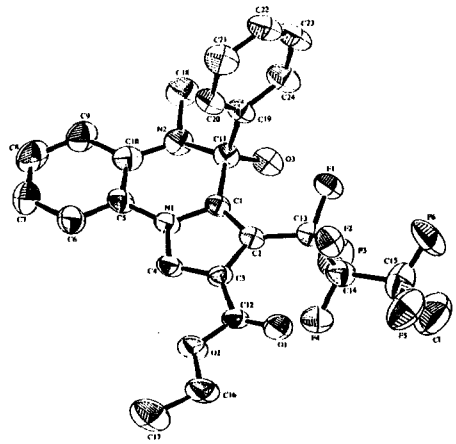


The formation of **3ae-3bg** may be depicted as shown in Scheme 1.

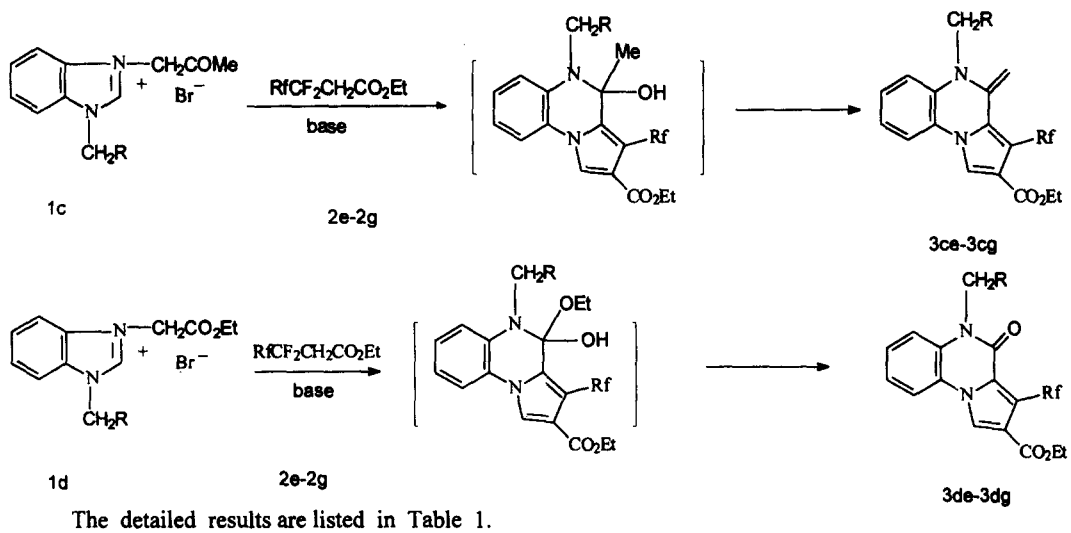


Scheme 1

In a similar way , N-acetonyl benzimidazole bromide (**1c**) and N-ethoxycarbonylmethyl benzimidazole bromide(**1d**) reacted with ethyl 2,2-dihydropoly(per)fluoro-alkanoate(**2**) to give 3-fluoroalkyl-4-methylene (**3ce-3cg**) and 3-fluoroalkyl 4-oxo (**3de-3dg**) pyrrolo[1,2-a]quinoxaline derivatives through the elimination of water and ethanol from the ring expansion intermediates respectively.



The X-ray structure of compound 3ae



The detailed results are listed in Table 1.

Table 1: The isolated yield of compounds **3ae—3df**.

1	R	Rf	Yield (%)
1a	H	$Cl(CF_2)_3$	3ae/60
1a	H	$Cl(CF_2)_5$	3af/86
1a	H	$F(CF_2)_7$	3ag/72
1b	Ph	$Cl(CF_2)_3$	3be/61
1b	Ph	$Cl(CF_2)_5$	3bf/85
1b	Ph	$F(CF_2)_7$	3bg/83
1c	Ph	$Cl(CF_2)_3$	3ce/75
1c	Ph	$Cl(CF_2)_5$	3cf/78
1c	Ph	$F(CF_2)_7$	3cg/76
1d	Ph	$Cl(CF_2)_3$	3de/75
1d	Ph	$Cl(CF_2)_5$	3df/71
1d	Ph	$F(CF_2)_7$	3dg/73

In conclusion, we have provided a new and simple approach to 3-fluoroalkyl-substituted pyrrolo[1,2-a]quinoxaline derivatives in high yield.

Typical procedure: A mixture of 1.1 mmol of N-phenacyl benzimidazole bromide (**1d**) in 4 ml DMF , 1 mmol ethyl 2,2-dihydropolyfluoroalkanoate (**2g**) and 3 mmol triethyl amine was stirred at 65 ° C for 4-5 hours . ^{19}F NMR spectra revealed that the reaction was completed . After cooling to room temperature , the mixture was poured into 1N aqueous HCl solution to make the final solution with Ph=5 . The solution was extracted with dichloromethane(3x25ml) . The organic phase was combined and washed with saturated brine , dried over anhydrous sodium sulfate . After removal of solvent, the residue obtained was purified by column chromatography using petroleum ether and ethyl acetate(5:1) as eluant to give the product (**3dg**) Anal. calcd. for $C_{28}H_{17}N_2O_3F_{15}$ C 47.07, H 2.40, N 3.92, F 39.89% found: C 47.05, H 2.21, N 3.79, N 3.79, F39.42%; ^1H NMR(300MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.79-7..23(m,9H), 5.54(s,2H), 4.40(q,2H), 1.42(t,3H); $^{19}FNMR$(56.4MHz, $CDCl_3$, $CFCl_3$ as the external standard) δ 79.8(s, 3F), 95.8(m, 2F), 116.8-125.8(m,10F); IR (ν cm-1) 1692(C=O), 1682(C=O), 1149-1267(C-F); MS 714(M^+, 8.75), 375(26.6), 91(100.0).

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