

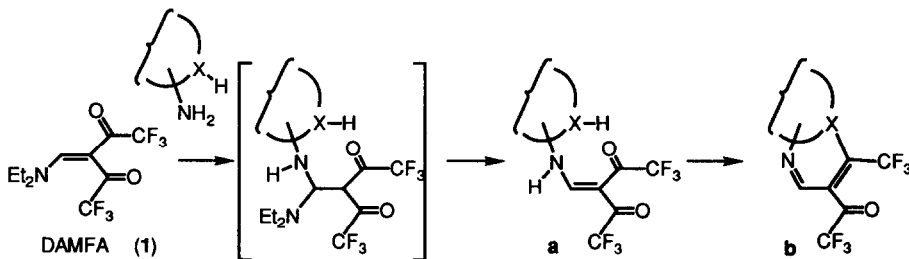
Synthesis of Some Fluorinated Nitrogen Heterocycles from (Diethylaminomethylene)Hexafluoroacetylacetone (*DAMFA*)

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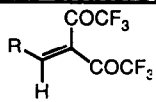
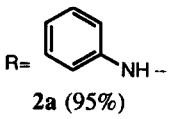
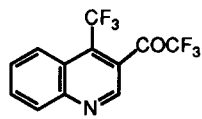
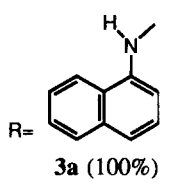
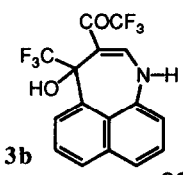
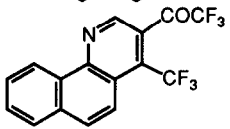
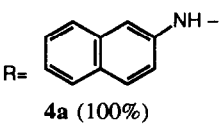
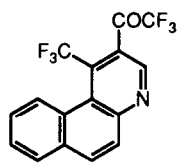
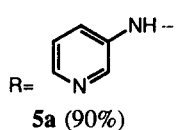
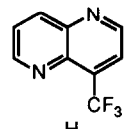
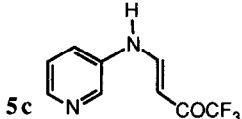
Abstract: Simple and highly efficient syntheses of the title compounds from *DAMFA* are described in the quinoline, azepinonaphthalene, azaphenanthrene(s), pyridopyridine, pyrazole, pyrrole and pyrimidine series.

The serendipitous observation of the oxidation of some alkaloidal tertiary amines with trifluoroacetic anhydride¹ had recently focused our attention to *N,N*-diethylaminomethylene-1,1,1,5,5,5-hexafluoroacetylacetone **1** (*DAMFA*), a compound prepared by Schreiber in 1980². Despite its highly reactive enaminodiketone pattern, surprisingly enough no mention of the use of *DAMFA* in the syntheses of heterocycles could be found in literature.



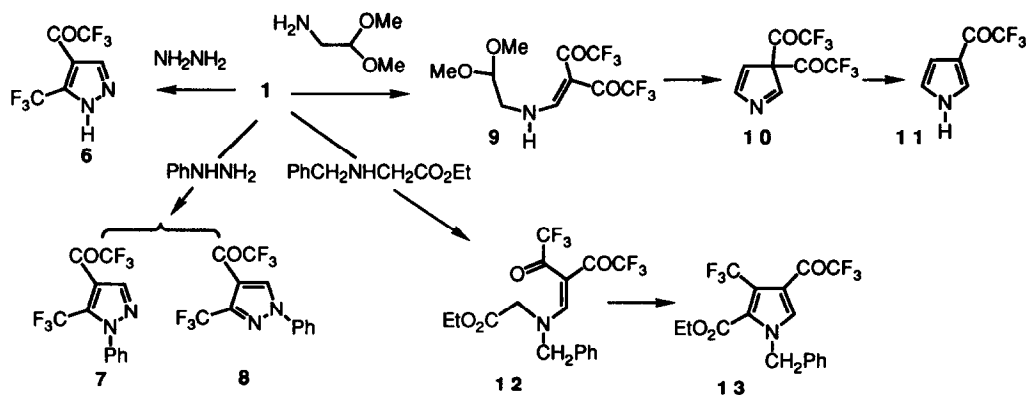
Scheme 1

Owing to the pharmacological interest in heterocycles bearing CF_3 appendages³, we studied the substitution of NEt_2 in *DAMFA* with various nitrogen nucleophiles, and the further cyclization of the resulting enamine-diones **a** to heterocycles **b** (Scheme 1).

<u>Enamine-diones(Yields)</u>	<u>Structures of Derivatives</u>	<u>Cyclization Conditions</u>	
		PPA	TiCl ₄
			
 2a (95%)	 2b	10%	96%
 3a (100%)	 3b	0%	90%
	 3c	15%	0%
 4a (100%)	 4b	-	100%
 5a (90%)	 5b	25%	60%
	 5c	0%	25%

Table

As expected, DAMFA easily suffered nucleophilic substitutions: prolonged treatments with primary amines in the presence⁴ of 0.1 eq of FeCl₃ gave the enamino-diketones **2a-5a** (Table) in 90 to 100% yields. Further cyclizations to nitrogen heterocycles were performed using protonic or Lewis acids. While heating **2a** in polyphosphoric acid (PPA) gave quinoline **2b** with a 10% yield only, the cyclization was made highly efficient (96%) upon treating a dichloromethane solution of **2a** with TiCl₄ (4-5 eq) for 14 h at room temperature. Compound **3a** from α -naphthylamine⁵ gave the azepinonaphthalene **3b** (90%) with TiCl₄, and the azaphenanthrene **3c** (15%) with PPA, probably reflecting a more hindered (enol phosphoric ester) intermediate in the last case. The isomeric azaphenanthrene **4b** was obtained (100%) from β -naphthylamine⁵ upon treatment of **4a** with TiCl₄. PPA treatment of **5a**, prepared from 3-aminopyridine, yielded the trifluorinated pyridopyridine **5b** (25%) while the TiCl₄ conditions improved the yield to 60% and disclosed the probable intermediacy of the β -mono-trifluoroacetylenamine **5c**.



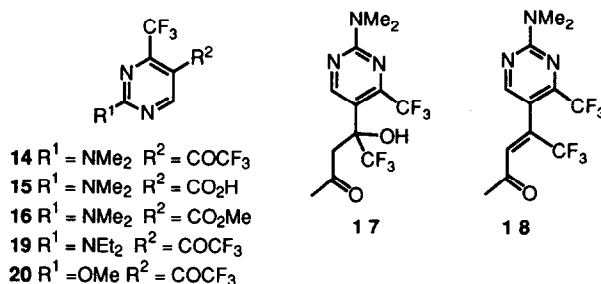
Scheme 2

Reaction of DAMFA with hydrazine in acetonitrile (rt, 4h) was straightforward yielding pyrazole **6** (96 %) (Scheme 2). Under similar conditions phenylhydrazine yielded both regioisomeric pyrazoles **7** (75 %) and **8** (25 %). The intermediate enehydrazine-diones were not isolated and the reaction proceeded smoothly in one step.

Turning to pyrroles, a synthesis by Okada⁶ using 1-ethoxy-2-trifluoroacetylene was conveniently adapted to DAMFA: enamine-dione **9** resulting from the reaction of **1** with 2,2-dimethoxyethylamine was treated with trifluoroacetic acid (TFA) and a few drops of water (rt, 4h). The intermediate 3,3-bis(trifluoroacetyl)pyrrolenine **10** lost one molecule of TFA in the reaction medium to generate 3-trifluoroacetylpyrrole **11** (83% from **1**), which had been actually described in Okada's paper.

Evans' efficient synthesis⁷ of porphobilinogen through the cyclization of an enamionone derived from an alkyl glycinate inspired a subsequent synthesis in the pyrrole series: reaction of DAMFA with ethyl N-benzylglycinate in MeCN (70°C, 4h) gave the enamine-dione **12**, which was not isolated and readily cyclized to the highly substituted pyrrole **13** (96%).

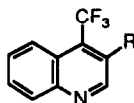
DAMFA was finally shown to react with urea derivatives, thus giving access to pyrimidines (Scheme 3):



Scheme 3

N,N-dimethylguanidine yielded pyrimidine **14** (MeCN, rt, 4h, 85 %), whose treatment with acetone in the presence of potassium carbonate incidentally gave aldol **17** (79 %), which was further dehydrated (methylene chloride, sulfuric acid, rt, 14h, 99 %) to enone **18**. Treatment of **14** with ethanolic KOH (rt, 4h)

followed by acidification quantitatively gave acid **15** while anhydrous methanol and potassium carbonate (rt, 24h) yielded ester **16** (85 %). Reaction of **1** with O-methylisourea in acetonitrile at room temperature was less straightforward, affording the diethylamino derivative **19** resulting from nucleophilic displacement of OMe by the diethylamine originating from DAMFA. However conducting the reaction at 65°C with continuous abstraction of the vapors allowed isolation of **20** with a 65 % yield. Transformation of **20** into nucleosidic analogues of thymidine is under current study.



21 R = CO₂H
22 R = H

Quinoline **2b** was similarly submitted to a haloform reaction (KOH, EtOH), which quantitatively gave 4-trifluoromethylquinoline-carboxylic acid **21** after careful neutralization, but suffered partial (60 %) decarboxylation to **22** upon acidification of the reaction medium to pH 1 and concentration under reduced pressure.

Acknowledgements

Spectral measurements by Dr D.Royer and Mr D.Patigny (NMR) and by Mr P.Sigaut (MS) are gratefully acknowledged. M.S. was partially supported by grants from the Moroccan government and from the University of Reims Champagne-Ardenne.

References and Notes

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