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Trifluoromethylated Heterocycles from β-Trifluoroacetyl-Lactams and -Benzolactams

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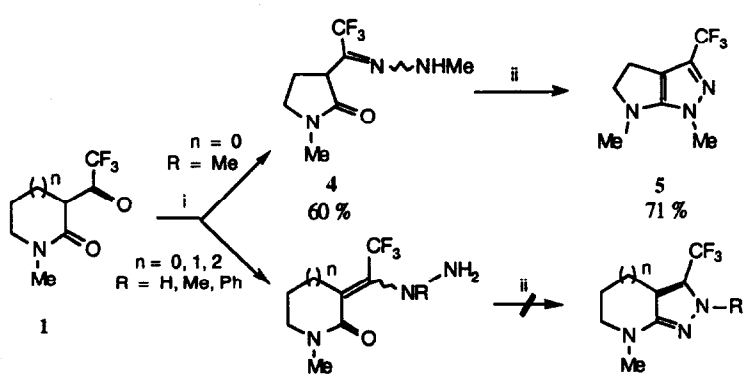
Abstract : Trifluoromethyl substituted heterocycles have been prepared by condensation of the new β-trifluoroacetyl-lactams **1** and -benzolactams **2** with methylhydrazine and benzamidine as bis-nucleophiles without opening of the lactam structure.

Because of their interesting biological activities, heterocyclic compounds bearing trifluoromethyl groups have become targets of choice in synthetic organic chemistry[1]. The starting materials should be inexpensive and carry the required trifluoromethyl group. Thus, trifluoroacetic acid and derivatives or ethyl trifluoroacetoacetate belong to the most readily accessible starting compounds for the construction of trifluoromethyl substituted heterocycles.

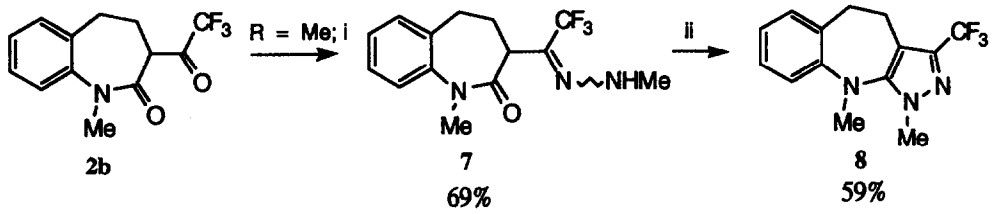
While trying to trifluoromethylate ethyl bromoacetate using CF_3CO_2Na/CuI in 1-methyl-2-pyrrolidinone (NMP) as solvent we noticed the formation of 3-(perfluorohydroxyisopropyl)-pyrrolidinone[2]. In order to check whether 3-trifluoroacetyl-NMP **1a** (n=0) is an intermediate, we had to develop a practical procedure[3] of its preparation since the literature method could not be duplicated[4]. We have also prepared β-trifluoroacetyl-lactams **1b,c** (n=1,2) and -benzolactams **2a,b** (n=1,2) using the same method[3]. Now we have examined these compounds in general as 1,3-bis-electrophiles for heterocyclisations with bis-nucleophiles such as hydrazines and amidines.

We were also intrigued by the question whether such heterocyclisations would proceed with or without opening of the lactam function.

As we found, 3-trifluoroacetyl-1-methyl-lactams **1a,b,c** and -benzolactam **2b** react with methylhydrazine to produce isolable hydrazones **4** and **7** which can be cyclised by treatment with phosphorus oxychloride without opening of the lactam ring (Scheme 1). In other cases, depending on the hydrazine substituent and the ring-size, enehydrazines **6** are formed but they do not cyclise under the same reaction conditions (Scheme 1).



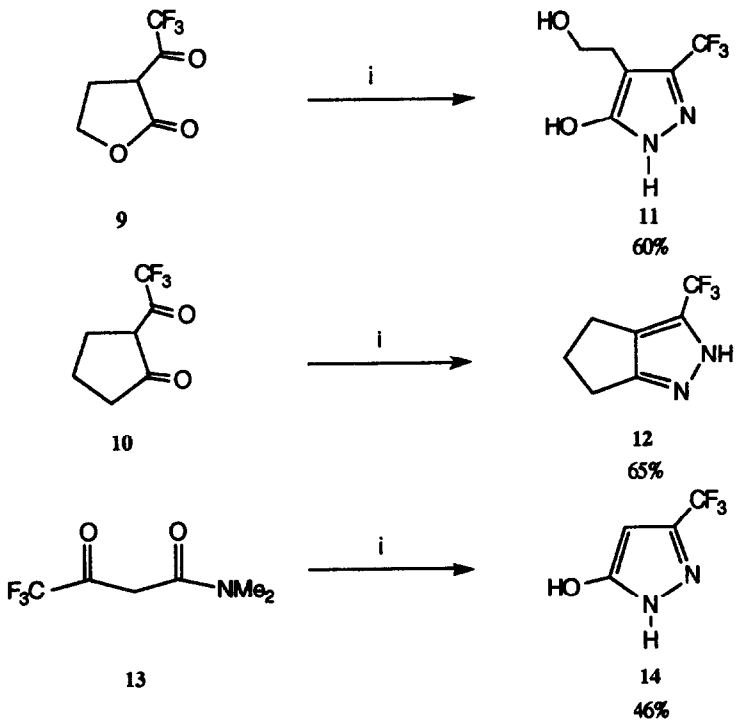
n = 0; R = H;Ph	74; 67%
n = 1; R = H;Me	70; 73%
n = 2; R = H;Me	73; 46%



i : $RNHNH_2$, APTS(cat), Ph-H reflux
ii : $POCl_3$, Pyr., CH_2Cl_2, 25°C

Scheme 1[5]

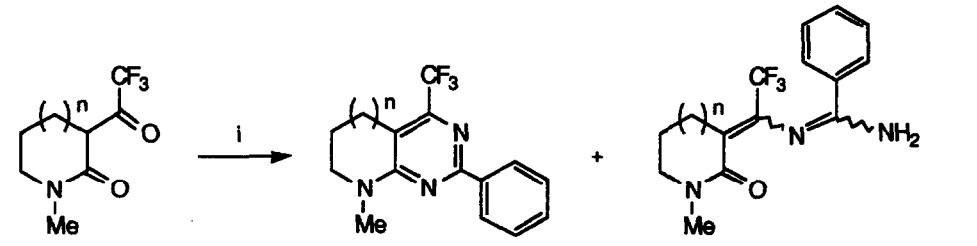
The comparison with related reagents is interesting. Thus, β-trifluoroacetyl-lactone 9[6] cyclises with hydrazine as 1,2-bis-nucleophile by ring-opening (Scheme 2), whereas the analogous α-trifluoroacetyl-cyclopentanone 10[6] cyclises as expected (Scheme 2). Furthermore, N,N-dimethyl-trifluoroacetoacetamide 13[6] also reacts normally with hydrazine by cyclisation followed by a loss of dimethylamine (Scheme 2).



i : $NH_2NH_2.H_2O$, APTS(cat), Ph-H reflux

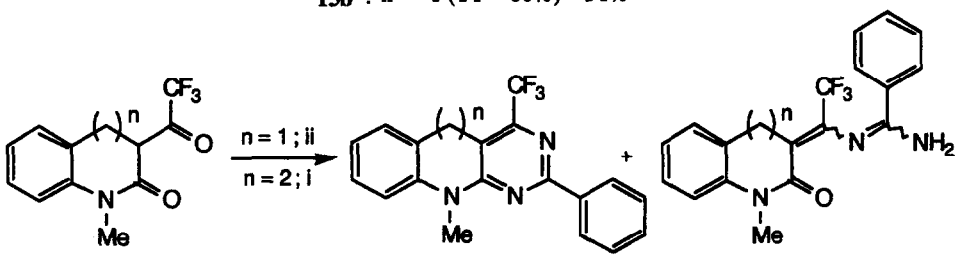
Scheme 2[7]

The reaction of benzamidine as 1,3-bis-nucleophile appears rather general since the annelated pyrimidine structures **15** and **16** arise from 3-trifluoroacetyl-lactams **1a,b** and -benzolactams **2a,b** (Scheme 3). The ring-open structures **17a** and **18b** (Scheme 3) are by-products in this reaction. They are reaction intermediates since they cyclise upon treatment with phosphorus oxychloride to trifluoromethylated pyrimidines **15a** and **16b**, respectively (Scheme 3).



1a,b **15a,b** **17a**

15a : n = 0 (TT = 49%) 28% 7%
15b : n = 1 (TT = 80%) 51% –



2a,b **16a,b** **18b**

16a : n = 1 (TT = 100%) 60% –
16b : n = 2 (TT = 92 %) 12% 35%

i : benzamidine, Δ, neat, 100-180°C
ii : benzamidine, Ph-Me reflux

Scheme 3[8]

The heterocycles **5, 8, 12, 15** and **16** represent new trifluoromethylated structures, whereas compounds **4, 6, 7, 17** and **18** possess an interesting trifluoromethyl hydrazone and azadiene function. The scope of these reactions and the problem of the regiochemistry with non-symmetrical hydrazines remain to be studied.

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References and notes

1. a) *Biomedicinal Aspects of Fluorine Compounds*; Filler, R.; Kobayashi, Y.; Eds; Elsevier, New York (1982); b) *Fluorine in Bioorganic Chemistry*; Welch, T.; Eswarakrishnan, S.; Eds; John Wiley & Sons, New York (1991).
2. Bouillon, J.-Ph.; Maliverney, C.; Merényi, R.; Viehe, H.G.; *J. Chem. Soc., Perkin Trans I*, **1991**, 2147-2149.
3. Preparation of β-trifluoroacetylated lactams **1a** (n=0), **1b** (n=1) and **2a** (n=1) : Lactam was treated first with 1.5 eq. of NaH in boiling THF followed by ethyl trifluoroacetate (1.5 eq.). For β-trifluoroacetylated lactams **1c** (n=2) and **2b** (n=2) : Lactam was treated with 1.3 eq. of lithium diisopropyl amide at -78°C followed by addition of ethyl trifluoroacetate (1.2 eq.) at -20°C.
4. Knunyants, I.L.; *Izv. Akad. Nauk. SSSR*, Ser. Khim., **1986**, *7*, 1688-1689.
5. All new compounds gave satisfactory spectroscopic data. Representative data for :
   6. : mp = 50-55°C (petroleum ether, CH_2Cl_2); IR (KBr) : 3260, 1665 and 1590 cm^{-1}; ^{19}F-NMR (reference for ^{19}F-NMR : $CFCl_3$) ($CDCl_3$) : δ_{CF_3} = -64.8 (s)
   7. : mp = 31-33°C (petroleum ether, diethyl ether); IR (KBr) : 1576 and 1561 cm^{-1}; ^{19}F-NMR ($CDCl_3$) : δ_{CF_3} = -62.5 (s)
6. The results for enehydrazines **6** will be reported soon.
   9. : mp = 110-113°C (petroleum ether, diethyl ether); IR (KBr) :3258, 1647, 1601, 1494 and 1461 cm^{-1}; ^{19}F-NMR ($CDCl_3$) : δ_{CF_3} = -70.1 (s)
   10. : mp = 85-86°C (petroleum ether, diethyl ether); IR (KBr) :1581, 1571, 1516 and 1491 cm^{-1}; ^{19}F-NMR ($CDCl_3$) : δ_{CF_3} = -62.5 (s)
   The products **9, 10** and **13** were already known in the literature. For **9** : Archer, S.; Perianayagam, C.; *J. Med. Chem.*, **1979**, *22*, 306-309. Allen, K.N.; Abeles, R.H.; *Biochemistry*, **1989**, *28*, 8466-8473. For **10** : Ebraheem, K.A.K.; Hamdi, S.T.; Khalaf, M.N.; *Can. J. Spectrosc.*, **1981**, *26*, 225-226. For **13** : Fomin, A.N.; Saloutin, V.I.; Rudaya, M.N.; Pashkewick, K.I.; *Zh. Org. Khim.*, **1986**, *22*, 1603-1609.
7. Compounds **11, 12** and **14** gave satisfactory spectroscopic data.
   13. : mp = 180-181°C (petroleum ether, AcOEt, MeOH); IR (KBr) : 3300, 3176 and 1634 cm^{-1}; ^{19}F-NMR ($CDCl_3$) : δ_{CF_3} = -61.9 (s)
   14. : mp = 129-130°C (petroleum ether, AcOEt); IR (KBr) : 3291, 3190, 1607, 1549 and 1501 cm^{-1}; ^{19}F-NMR (CD_3OD) : δ_{CF_3} = -61.4 (s)
   15. : Gilman, H.; Tolman, L.; Yeoman, F.; Woods, L.A.; Shirley, D.A.; Zvakian, S.; *J. Am. Chem. Soc., 1946, 68*, 426-428; mp = 215°C (petroleum ether, diethyl ether); IR (KBr) : 3289, 3196 and 1603 cm^{-1}; ^{19}F-NMR ($CDCl_3$) : δ_{CF_3} = -61.1 (s)
8. All compounds in scheme 3 are characterized by IR, ^{1}H-NMR, ^{19}F-NMR, ^{13}C-NMR and MS.

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