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Cosmas O. Okoro
Tennessee State University

Mumiye A. Ogunwale
Tennessee State University

Tasneem Siddiquee
Tennessee State University

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Article

Synthesis of Some New Fluorinated Hexahydroquinoline and Acridinedione Derivatives in Trifluoroethanol

Cosmas O. Okoro *, Mumiye A. Ogunwale and Tasneem Siddiquee

Department of Chemistry, Tennessee State University, Nashville, TN 37209, USA;
E-Mails: mumiye828@yahoo.com (M.A.O.); tsiddiqu@tnstate.edu (T.S.)

* Author to whom correspondence should be addressed; E-Mail: cokoro@tnstate.edu;
Tel.: +1-615-963-5325; Fax: +1-615-963-5326.

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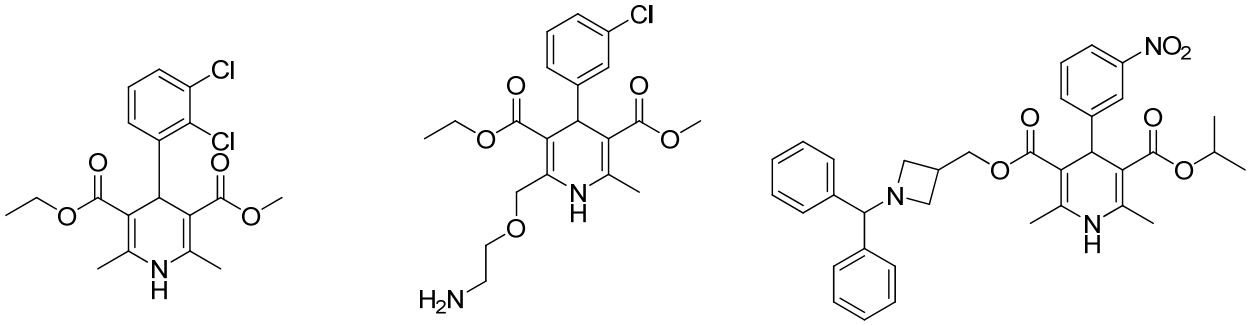
Abstract: This article describes one-pot synthesis of new fluorinated hexahydroquinoline derivatives via unsymmetric Hantzsch reaction involving 5-trifluoromethyl-1,3-cyclohexanedione, aldehydes, acetoacetate ester, and ammonium acetate in trifluoroethanol (TFE). The reaction is simple and rapid with high yield.

Keywords: unsymmetric Hantzsch reaction; dihydropyridine; trifluoromethyl; hexahydroquinoline; acridinedione; trifluoroethanol

1. Introduction

Substituted 1,4-dihydropyridines (1,4-DHPs) are analogs of nicotine adenine dinucleotide dehydrogenase (NADH) coenzymes and are an important class of drugs [1]. In recent years, attention has been paid to the synthesis of 1, 4-dihydropiridines due to their significant biological activities [2]. They are well known as calcium channel modulators and have emerged as an important class of drugs for the treatment of cardiovascular diseases [3]. In particular, dihydropyridine drugs, such as nifedipine, nicardipine, amlodipine are effective cardiovascular agents for the treatment of hypertension [4]. Due to their ability to block the L-type calcium channel, DHPs, such as felodipines have been characterized as potentiators of several mutant cystic fibrosis transmembrane conductance regulator (CFTR) channels [5]. In addition, dihydropyridine unit has been used as a hydride source for reductive amination [6].

Examples of 1,4-Dihydropyridine drugs.

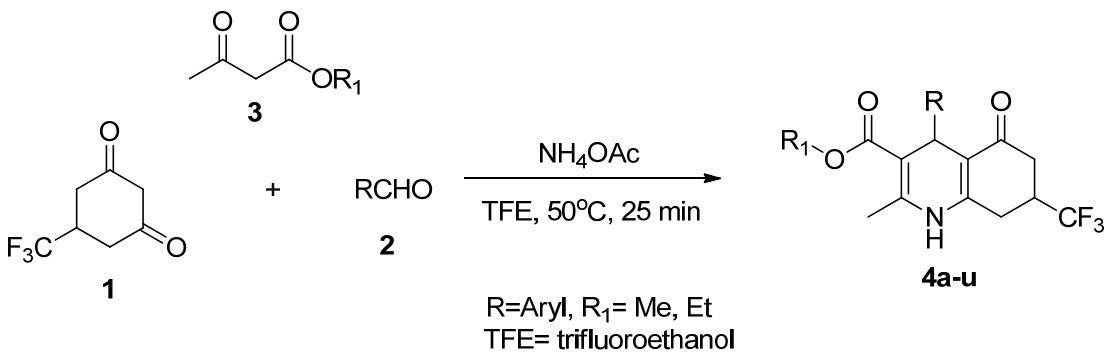


Heterocyclic ring system, such as acridinedione is generally considered to be among the most prevalent ring systems in medicinal chemistry [7]. They are known to be potent frameshift mutagens in virus and bacteria [8]. Acridinediones have also been reported as antimalarial agents [9].

Organic compounds bearing trifluoromethyl group have attracted considerable attention due to their role in organic, medicinal, and heterocyclic synthesis. In particular, the incorporation of fluorine atom has been used by medicinal chemists to tailor the physical and metabolic profiles of drug candidates [10]. For instance, addition of fluorine in the place of hydrogen has been known to enhance binding interactions, improve metabolic stability, increase CNS penetration, and eliminates ancillary ion channel activity by attenuating amine basicity [11]. The electronic effect of fluorine via induction is enormous and this change could have a major effect on the binding potential of the small molecules.

Polycyclic compounds, particularly heterocycles are important in medicinal chemistry because their rigid structures permit selective interaction with proteins and other receptors. The literature has few reports of dihydropyridines containing the highly electronegative and lipophilic trifluoromethyl group. Thus, the synthesis of trifluoromethylated heterocyclic compounds has drawn much attention in recent years. In continuation of our efforts towards the synthesis of fluorinated heterocycles of biological importance, we turned our attention to the synthesis of fluorinated hexahydroquinoline derivatives in trifluoroethanol (Scheme 1), as potential calcium channel modulators. We chose 2,2,2-trifluoroethanol because the solvent appears to have low nucleophilicity, strong hydrogen bond donating ability and high polarity [12]. It is also cheap and relatively nontoxic.

Scheme 1. Synthesis of fluorinated hexahydroquinoline from 5-trifluoromethyi-1,3-cyclohehexanedione, aldehydes, β- ketoesters and ammonium acetate.



2. General

Apart from 5-trifluoromethyl-1,3-cyclohexanedione that was discovered by our group [13], the reagents and solvents in the appropriate grades were purchased and used without further purification. Melting points were done on Mel-temp LL and were uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum One FT spectrometer. ^{1}H and ^{13}C were recorded in $CDCl_3$ on Oxford NMR (300 MHz) instrument using TMS as internal standard. The elemental analysis was carried out on Perkin Elmer 2400 Elemental Analysis (C-H-N). The single crystal X-ray diffraction of **4d** was performed on the Rigaku XtaLAB Mini.

General Procedure for synthesis of compounds 4a–u: 5-(trifluoromethyl)-1,3-cyclohexanedione (1 mmol), acetoacetate ester (1 mmol) aldehyde (1 mmol), ammonium acetate (1 mmol) were dissolved in 2 mL of TFE and stirred at 50 °C. The reaction progress was monitored by TLC and TFE was removed at the end of the reaction by distillation. The crude product was purified by recrystallization from ethanol with a few drops of water to afford pure fluorinated hexahydroquinoline derivatives.

General Procedure for synthesis of compounds 5a–b: A mixture of 5-(trifluoromethyl)-1,3-cyclohexanedione (2 mmol), aldehyde (1 mmol), ammonium acetate (1 mmol), were dissolved in 2 mL of TFE and stirred at 50 °C for 50 min. The progress of the reaction was monitored by TLC. The crude product was purified by recrystallization from ethanol to afford pure fluorinated acridinedione **5a-b**.

The spectroscopic data of selected compounds are shown below.

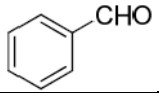
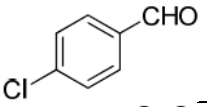
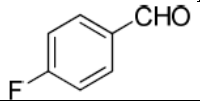
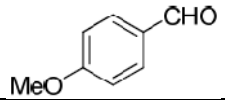
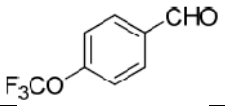
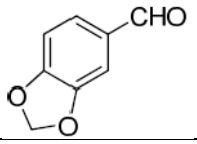
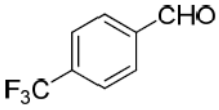
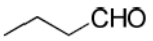
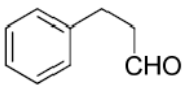
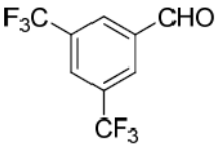
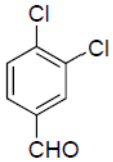
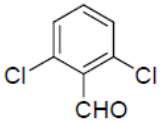
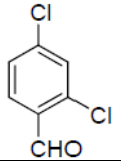
4-(4-chlorophenyl)-2-methyl-5-oxo-7-trifluoromethyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (4d): mp = 258–259 °C, ^{1}H NMR 300 MHz, $CDCl_3$: δ = 1.28 (t, J = 7.2 Hz, 3H), 1.65 (s, 3H), 2.55–2.80 (m, 1H), 4.05 (q, J = 7.2, 2H), 5.01 (s, 1H), 6.60 (s, 1H, NH), 6.77 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), ^{13}C NMR (300 MHz $CDCl_3$): δ = 14.2, 19.1, 19.6, 25.9, 32.8, 41.4, 61.7, 102.3, 112.0, 128.7, 130.5, 131.2, 137.5, 142.2, 150.7, 167.7, 198.8; IR (KBr, cm^{-1}) 3287, 3209, 3088, 2950, 1708, 1610; MS m/z: 75 (5%), 303 (100%), 413 (M^+, 55%); Anal. Calc for $C_{20}H_{19}ClF_3NO_3$: C, 58.05; H, 4.63; N, 3.38%. Found: C, 57.02; H, 4.60; N, 3.40%.

9-(4-fluorophenyl)-3,6-bis(trifluoromethyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (5a): mp > 300 (decomposes), ^{1}H NMR 300 MHz, $CDCl_3$): δ = 1.36–2.81 (m, 8H, cyclohexyl-Hs), 2.81 (m, 4H), 2.99 (m, 2H, CH next to CF_3), 4.82 (s, 1H, CH), 7.10–7.21 (m, J = 8.0, 4H, Ar-H), 8.53 (s, 1H, NH); ^{13}C NMR (300 MHz $CDCl_3$): δ = 19.8, 25.8, 33.0, 111.9, 115.2, 130.7, 137.5, 140.0, 149.3, 160, 198.9; IR(Nujol, cm^{-1}): 3436 (NH), 1653 (O=C–C=C–NH). MS m/z: 75(5%), 353 (100%), 447(M^+, 50%). Calc for $C_{21}H_{16}F_7NO_2$: C, 56.38; H, 3.61; N, 3.13%. Found: C, 56.35; H, 3.66; N, 3.15%.

3. Results and Discussion

In an initial endeavor, we carried out the asymmetric Hantzsch reaction by condensing equimolar amount of 5-trifluoromethyl-1,3-cyclohexanedione, methylacetoacetate, unsubstituted benzaldehyde and ammonium acetate at 50 °C in trifluoroethanol. The reaction reached completion in 25 min (monitored by tlc) with 98% yield. Next, we extended the reactions using substituted aromatic aldehyde. The reactions were complete in 25 min as before with excellent yield regardless of the nature of the substituents on the aromatic ring. However when the reaction was carried out using butyraldehyde, the reaction was over in 50 min albeit in lower yields (entries 15, 16, Table 1)

Table 1. List of Compounds Synthesized and their percent yields.

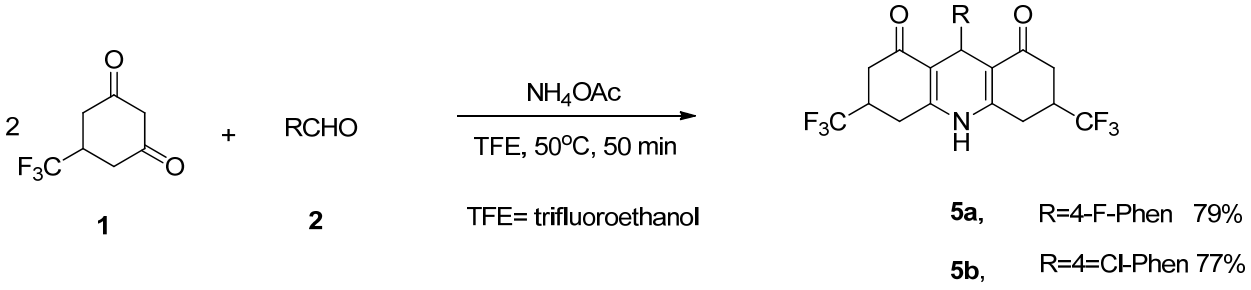
Entry [a]	R	R_1	Product	Yield (%) [b]
1		**Me**	**4a**	98
2		**Et**	**4b**	92
3		**Me**	**4c**	91
4		**Et**	**4d**	90
5		**Me**	**4e**	90
6		**Et**	**4f**	89
7		**Me**	**4g**	95
8		**Et**	**4h**	96
9		**Me**	**4i**	97
10		**Et**	**4j**	93
11		**Me**	**4k**	99
12		**Et**	**4l**	91
13		**Me**	**4m**	97
14		**Et**	**4n**	84
15		**Me**	**4o**	79
16		**Et**	**4p**	72
17		**Me**	**4q**	90
18		**Me**	**4r**	90
19		**Et**	**4s**	97
20		**Et**	**4t**	98
21		**Et**	**4u**	97

[a] All reactions proceeded to completion

[b] Yield after recrystallization

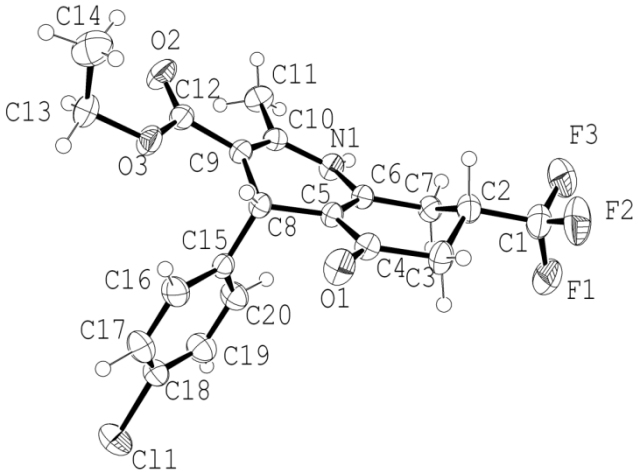
Upon completion of the synthesis of fluorinated hexahydroquinoline derivatives, we explored the synthesis of hexahydroacridinedione under similar conditions (Scheme 2 below). The reaction of two equivalents of 5-trifluoromethyl-1,3-cyclohexanedione with one equivalent each of aromatic aldehyde and ammonium acetate proceeded with good yield to give 5a and 5b, as shown in Scheme 2.

Scheme 2. Synthesis of fluorinated hexahydroacridinedione from 5-trifluoromethyi-1,3-cyclohehexanedione, aldehydes, and ammonium acetate.



The Infra-red spectra of all the products showed intense signals for carbonyl (1740–1690 cm^{-1}) and NH (3500–3300 cm^{-1}) functional groups. The detailed results are given in Table 1. The structure of **4d** was established by single crystal X-ray analysis (Figure 1) [12] and IR, NMR, and elemental analysis. The crystal data has been deposited in the Cambridge Crystallographic Data Center as supplementary publication number, CCDC 843861. This is the first report of such synthesis using 5-trifluoromethyl-1,3-cyclohexanedione, rather than dimedone.

Figure 1. ORTEP diagram of the single-crystal X-ray structure of 4d [14].



4. Conclusions

In summary, we have described the synthesis of some new trifluoromethylated hexahydroquinoline and acridinedione derivatives via Hantzsch route using 5-trifluoromethyl-1,3-cyclohexanedione as a CF_3-building block. The reaction conditions are mild, yields are high; reaction time is short; product isolation and purification are easy; and the overall process is cost effective and easy to handle. All the products are new and represent synthetically useful compounds for further elaboration. The

biological evaluation of these compounds will be investigated in the future and will be published in specialized journals.

Acknowledgments

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Conflict of Interest.

There is no Conflict of Interest

References and Notes

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14. X-ray diffraction studies were performed at room temperature on a pale yellow crystal of **4d** of approximate 0.57 × 0.52 × 0.36 mm dimensions. All measurements were made on a Rigaku Mercury375R/M CCD (XtaLAB mini) diffractometer using graphite monochromated Mo-Kα radiation. Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell (space group P21/n) with dimensions: a = 11.8544(10) Å, b = 13.9622(12) Å, c = 12.5692(11) Å and β = 110.300(8)°. *Data reduction*: of the 20341 reflections that were collected, 4477 were unique (R_{int} = 0.0212). Data were collected and processed using CrystalClear [a] (Rigaku). The linear absorption coefficient, μ, for Mo-Kα radiation is 2.435 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.796 to 0.916. The data were corrected for Lorentz and polarization effects. *Structure Solution and Refinement*: The structure was solved by direct methods [b] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 4477 observed reflections and 269 variable parameters and converged (largest parameter shift was 0.12 times its esd) with unweighted and weighted agreement factors of: R1 = 0.0490 and wR2 = 0.1938. This was conducted using the program suiteWINGX [c].
(a) *CrystalClear:* Rigaku Corporation, 1999. CrystalClear Software User's Guide, Molecular Structure Corporation, ©2000. Pflugrath, J.W. *Acta Cryst.* **1999**, *D55*, 1718–1725.
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