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Silicon tetrachloride-induced green and efficient MCR protocol for the synthesis of 1,8-dioxo-decahydroacridines and their transformation to novel functionalized pyrido-tetrazolo[1,5-a]azepine derivatives

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ABSTRACT

Green and efficient MCR protocol for the synthesis of 1,8-dioxo-decahydroacridine derivatives was achieved through a one-pot, three-component condensation of dimedone, aryl amines and aryl aldehydes utilizing tetrachlorosilane (TCS) as catalyst under solvent-free conditions. Reaction of the titled compounds with TCS-NaN_3 to give novel functionalized pyrido[3,2-c]tetrazolo[1,5-a]azepine derivatives is also described.

KEYWORDS

Tetrachlorosilane; 1,8-Dioxo-decahydroacridines; Solvent-free synthesis; Pyrido-tetrazolo[1,5-a]azepines.

INTRODUCTION

1,8-Dioxo-decahydroacridines are polyfunctionalized 1,4-dihydropyridine derivatives (DHPs), a class of nitrogen heterocycles of broad spectrum of important biological properties and pharmaceutical applications[1]. For example, DHPs act as potential drugs in treatment of congestive heart failure[2] and possess antimicrobial[3], anti-tuberculosis[4], anti-oxidant[5], and anti-tumor activities[6]. 1,8-Dioxodecahydroacridines are known as laser dyes[7] and a number of them possess antimicrobial activity[8] and act as sirtuins inhibitors[9]. Synthesis of 1,8-dioxo-decahydroacridines is generally achieved by multi-component coupling reaction (MCR) of 5,5-dimethyl-1,3-cyclohexadione, aromatic aldehydes and amines using Lewis or Bronstedacid catalysts[10]. Nevertheless, some of these protocols are disadvantageous in terms of readily unavailability of catalyst, long reaction times or using thermal conditions at elevated temperature. Therefore, efforts for improving this synthesis viaeco-friendly, economic, and convenient catalyzed-protocols are still relevant. On the other hand, tetrazoles are very useful compounds in medicinal chemistry and important synthetic intermediates[11]. For example, they have been considered as surrogates for the cis-amide bonds, making it a valuable tool in the design of conformationally-constrained peptidomimetics[12], they are also known as HIV-protease inhibitors[13] as well as cyclooxygenase-2 (COX-2) inhibitors[14]. In addition, there are a lot of biologically active substances among their fused analogs such as tetrazolo[1,5-*a*]quinolines[15], tetrazolo-pyrimidines[16], tetrazolo[5,1-a]phthalazines[17], and tetrazolo[1,5-c]quinazolines[18]. Moreover, some tetrazole derivatives are of the best-selling 5-membered ring heterocyclic pharmaceuticals. For example, Losartan[19], an angiotensin II antagonist which is commonly used for treatment of hypertension

and Cilostazol[20], a 1,5-disubstituted tetrazole, used as a platelet aggregation inhibitor are in the top selling 200 drugs[21](Figure 1).

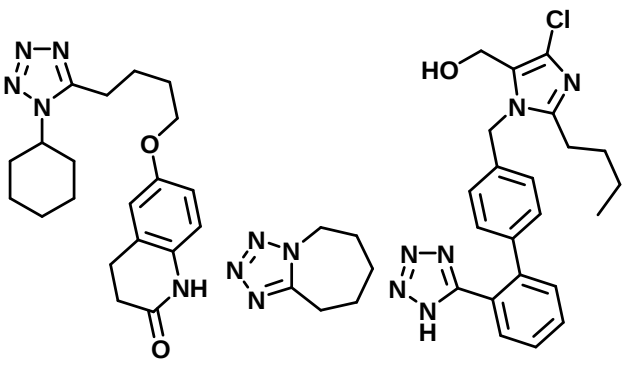


Figure 1 : Examples of some tetrazole-based drugs

In conjunction with our interest[22] in exploring the utility of tetrachlorosilane (TCS)[23] in organic synthesis, we report herein a facile green and mild procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives in high yields through a one-pot three-component reaction of dimedone, aryl amines and various aromatic aldehydes catalyzed by the inexpensive and readily available tetrachlorosilane under solvent-free conditions. Transformations of the prepared 1,8-dioxo-decahydroacridine derivatives into novel functionalized pyrido-bistetrazolo[1,5-a]azepine derivatives were also accomplished through their reactions with $SiCl_4$-NaN_3[24-26].

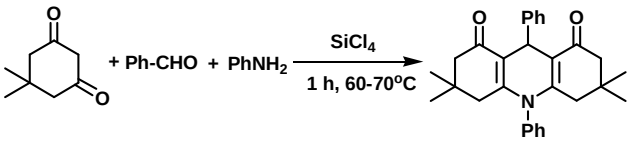
RESULTS AND DISCUSSION

The multi-component reaction of dimedone (**1**, 2 mole), benzaldehyde (**2a**, 1 mole) and aniline (1.2 mole) in the presence of $SiCl_4$ was studied as a model reaction. An optimized study of the reaction conditions has shown thatonly 10mol% of $SiCl_4$ was enough to achieve the reaction product in the highest yields at 60-70°C for 1h, under neat conditions (TABLE 1, entry 2).

The MCR of dimedone, aniline derivatives and aromatic aldehydes in the presence of $SiCl_4$ works well giving excellent yields of respective 1,8-dioxo-decahydroacridines under solvent-free conditions. (Scheme 1, TABLE 2).

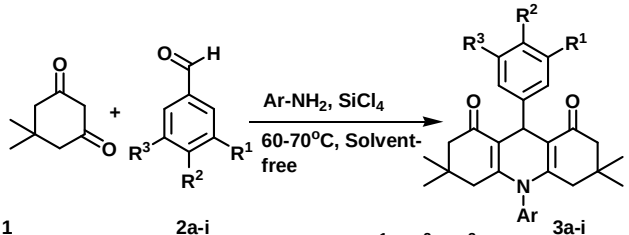
The general process was examined through applying the reaction conditions to various aromatic aldehydes bearing either electron donating groups (such as methyl, mono or tri methoxy groups) or moderately electron-withdrawing groups (such as, cyano and halide). However, the reaction with aldehydes bearing

TABLE 1: Optimization of the amount of tetrachlorosilane



Entry	$SiCl_4$ (mole %)	Yield (%)[a]
1	00	22
2	10	87
4	20	81
5	30	67

[a] **Isolated yield**



1 2a-i 3a-i

2a, 3a; Ar = Ph, $R^1 = R^2 = R^3$= H
2b, 3b; Ar = Ph, $R^1 = R^3$= H, R^2 = Cl
2c, 3c; Ar = Ph, $R^1 = R^3$= H, R^2= Br
2d, 3d; Ar = Ph, $R^1 = R^3$= H, R^2= Me
2e, 3e; Ar = Ph, $R^1 = R^3$= H, R^2= OMe
2f, 3f; Ar = 4-$MeOC_6H_4$-, $R^1 = R^3$ = H, R^2= Cl
2g 3g; Ar = 4-MeC_6H_4-, $R^1 = R^3$= H, R^2 = Cl
2h, 3h; Ar = 4-MeC_6H_4-, $R^1 = R^2 = R^3$= OMe
2i, 3i; Ar = 4-MeC_6H_4-, $R^1 = R^3$= H, R^2 = CN

Scheme 1 : Syntheis of 1,8-dioxo-decahydroacridines

TABLE 2 : TCS - Catalyzed synthesis of 1,8-dioxo-decahydroacridines

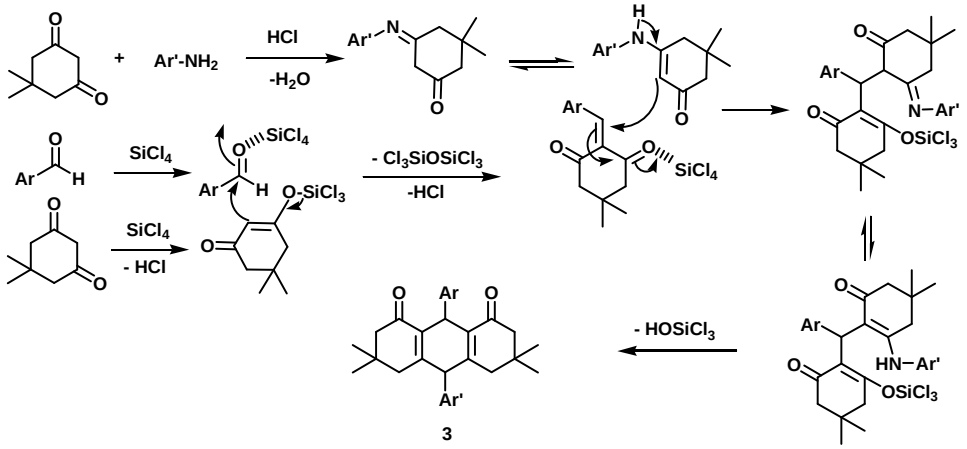
Entry	Aldehyde	Amine	Time (h)	Product	Yield (%)[a]
1	Benzaldehyde	Aniline	1	**3a**	87
2	4-Chlorobenzaldehyde	Aniline	1	**3b**	80
3	4-Bromobenzaldehyde	Aniline	1.5	**3c**	81
4	4-Methylbenzaldehyde	Aniline	2	**3d**	91
5	4-Methoxybenzaldehyde	Aniline	2	**3e**	90
6	4-Chlorobenzaldehyde	*p*-Anisidine	1.5	**3f**	92
7	4-Chlorobenzaldehyde	*p*-Toluidine	1	**3g**	83
8	3,4,5-Trimethoxybenzaldehyde	*p*-Toluidine	1	**3h**	85
9	4-Cyanobenzaldehyde	*p*-Toluidine	1	**3i**	82
10	4-Nitrobenzaldehyde	Aniline	1	**3j**[(b)]	83
11	4-Nitrobenzaldehyde	*p*-Toluidine	1	**3k**[(b)]	81

[a] **Isolated yield;** [b]**Dioxo-octahydroxanthene derivative**

strongly electron-withdrawing group (such as, nitro) gave exclusively the 1,8-dioxoxanthene derivative (TABLE 2, entries 10 and 11). In all cases studied, the respective 1,8- dioxo-decahydroacridines were obtained in good to excellent isolated yields. The structure of isolated 1,8-dioxo-decahydroacridine derivatives was assigned based on their spectral analyses as well as by matching their melting points with reported analogues[10].

As depicted in scheme 2, the mechanism of synthesis of acridinederivatives **(3)** has been proposed through a $SiCl_4$-catalyzed cascade Knovenagel condensation-nucleophilic addition and cyclization resembling the well-documented Hantzsch-type reaction[10j,k].

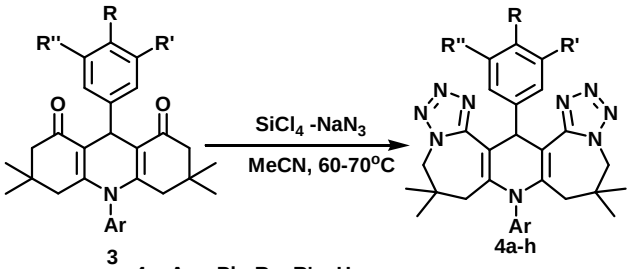
Owing to the well-documented medicinal importance of both DHPs[1] and potential drugs related to the terazolo[1,5-a]azepine core structure, e.g. Pentetrazol (PTZ) [27] (Figure 1),we thought that combinations of pharmacologicallyactive DHPs with a tetrazole moiety may increase their biological activity or create new medicinal properties.Thus, we pursued studying reaction of the prepared 1,8-dioxo-decaahydroacridines with silylazides (formed in situ by a reaction of TCS with NaN_3) envisaging the formation of novel tetrazoloazepines including dihydropyridine core structure for biological evaluation. To our delight, the reaction of 1,8-dioxo-decahydroacridines with TCS-NaN_3 according to the well-documented procedure [24-26]



Scheme 2 : A plausible mechanism for the formation of 1,8-dioxo-decahydroacridines

led to a smooth formation of novel functionalized pyrido-bis[3,2-c]tetrazolo[1,5-a]azepines in very good yields. However, the reaction can proceed at room temperature over a long time (12 h), it was more convenient to conduct the reaction at 60-70°C, which shortened the reaction time to 1h (Scheme 3, TABLE 3).

The structure elucidation of tetrazoloazepines **(4)** was performed on the basis of both elemental and spectral analyses. In the IR spectra, the products displayed a characteristic C=N stretching band at ν_{max} 1652-1655 cm^{-1}, supporting the formation of bis-tetrazole. The ^{1}H-NMR spectra of bis-tetrazoloazepines were in agreement with the depicted structures.For example, the ^{1}H NMR spectra of **(4c)** showed a singlet at δ 5.74 ppm attributed to the methine proton (CH) andtwo characteristic quartets of integration corresponding to four protons each, atδ4.0-4.12 and 2.04-2.21ppm. These two quartets are most likely attributed to the protons at carbon attached to the nitrogen (2 x N-CH_2) and allylic protons (2 x CH_2-C=C) respectively.Furthermore, mass spectrum of **4c**displayed two peaks at *m/z* 606 and 608 of almost equal intensity (due to bromine iso-



4a; Ar = Ph, R = R' = H
4b; Ar = Ph, R = Cl, R' = R'' = H
4c; Ar = Ph, R = Br, R' = R'' = H
4d; Ar = Ph, R = Me, R' = R'' = H
4e; Ar = Ph, R = OMe, R' = R'' = H
4f; Ar = 4-MeOC$_6$H$_4$-, R = Cl, R' = R'' = H
4g; Ar = 4-MeC$_6$H$_4$-, R = Cl, R' = R'' = H
4h; Ar = 4-MeC$_6$H$_4$-, R = R' = R'' = OMe

Scheme 3 : Synthesis of aryl-pyrido-bis-tetrazoloazepine derivatives

topes) corresponding in mass to its molecular ion $(M+Na)^+$. The simplicity, mild conditions, cheap and ease of reagent handling and toleration to diverse substrates are features of the present synthetic procedure.

TABLE 3 : TCS – NaN_3 Mediated syntheis of aryl-pyrido-bis-tetrazoloazepine derivatives

Entry	R R' R''	Ar	Time (min)	Product	Yield (%)[a]
1	H HH	Ph	60	**4a**	87
2	Cl H H	Ph	40	**4b**	85
3	Br H H	Ph	35	**4c**	93
4	Me H H	Ph	50	**4d**	91
5	OMe H H	Ph	50	**4e**	95
6	Cl H H	4-$MeOC_6H_4$-	60	**4f**	96
7	Cl H H	4-MeC_6H_4-	45	**4g**	88
8	OMeOMeOMe	4-MeC_6H_4-	60	**4h**	92

[a]**Isolated yield**

EXPERIMENTAL

General

Melting points were determined using a Buchi melting point M 565 apparatus and are uncorrected. The IR spectra were recorded with Mattson FTIR spectrometer 5000. Absorption maxima were measured in cm^{1}. The NMR spectra were recorded with Bruker 300 MHz spectrometer instrument in $CDCl_3$. The chemical shifts (δ) were measured in ppm. Mass spectra were recorded on a Agilent LC-MS spectrometer (pump quarter nary 1200 Series, quadrupole MSD 6110). LC column into multimode (ESI+APCI) ion source of MSD. Columnchromatography was performed on silica gel (100-200 or 200-300 mesh) using petroleum ether and ethyl acetate as eluent. Thin layer chromatography (TLC) was performed on Merck silica gel GF254 plates and visualized by UV-light (254 nm) and iodine. Tetrachlorosilane was used as obtained from commercial sources and used without further purification.

Typical procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives:

To a stirred mixture of aldehyde (5 mmol), dimedone (10 mmol) and aryl amine (6 mmol), a catalytic amount of $SiCl_4$ (1.5 mmol, 0.18mL) was added and the reaction mixture was vigorously stirred at 60-70°C with exclusion of moisture. On completion (the reaction was monitored by TLC), the mixture was quenched with cold water, extracted with EtOAc, dried over anhydrous $MgSO_4$ and the solvent was vaporized under vacuum and the residue was recrystallized from EtOH to give pure **(3)**. The decahydroacridinediones**3** except for **(3h)**, are known compounds and all spectroscopic data were in agreement with literature.

Data for **(3h)**: Mp = 226°C; IR (KBr, cm^{-1}): ν 3043, 2955, 2936, 1641, 1574, 1508, 1361, 1218, 1096, 921, 734; ^{1}HNMR (300 MHz, $CDCl_3$):δ 7.33 (d, *J* = 9 Hz, 2H, Ar-H), 7.05 (d, *J* = 9 Hz, 2H, Ar-H), 6.69 (s, 2H, Ar-H), 5.26 (s, 1H, CH), 3.81 (s, 6H, 2 x OCH_3), 3.77 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3), 2.07-2.20 (m, 6H), 1.84 (d, *J* = 18 Hz, 2H), 0.96 (s, 6H, 2 x CH_3), 0.86 (s, 6H, 2 x CH_3);EI-MS: 552 $(M+Na)^+$;Anal. Calcd. For$C_{33}H_{39}NO_5$ (529.28):C, 74.83; H, 7.42; N, 2.64. Found: C, 74.97; H, 7.31, N, 2.49.

Synthesis of aryl-pyrido[3,2-c]tetrazolo[1,5-a]azepine derivatives:

A typical procedure for the reaction of **3** with $SiCl_4$/NaN_3 in the ratio 1:2:6, to give **(4)** : To a stirring mixture of **3** and NaN_3 in CH_3CN at room temperature was added $SiCl_4$ and the mixture warmed at 60-70°C with stirring until TLC showed disappearance of the starting material. The reaction was then poured into aq. $NaHCO_3$ solution and the mixture was extracted with EtOAc. The extracts were dried over $MgSO_4$ and concentrated, cooled to give pure **(4)**.

Data for **(4c,e,h)** as representative examples are showed: **(4c)**:Mp = 270°C; IR (KBr, cm^{-1}): ν 2959, 2926, 2869, 1654, 1597, 1283, 1095, 728, 512; ^{1}HNMR (300 MHz, $CDCl_3$):δ 7.55 (m, 3H, Ar-H), 7.42 (d, *J* = 6 Hz, 4H, Ar-H), 7.21 (m, 2H, Ar-H), 5.74 (s, 1H, CH), 4.06 (q, *J* = 12 Hz, 4H, 2 x N-CH_2), 2.12 (q, *J* = 15 Hz, 4H, 2 x CH_2), 1.03 (s, 6H, 2 x CH_3), 0.84 (s, 6H, 2 x CH_3);EI-MS: 608, 606 $(M+Na)^+$;Anal. Calcd. For$C_{29}H_{30}BrN_9$ (583.18):C, 59.59; H, 5.17; N, 21.57. Found: C, 59.43; H, 5.28, N, 21.39.

For **(4e)**:Mp = 255°C; IR (KBr, cm^{-1}): ν 2960, 2926, 1653, 1608, 1509, 1372, 1251, 1117, 791, 633; ^{1}HNMR (300 MHz, $CDCl_3$):δ 7.53 (m, 3H, Ar-H), 7.43 (d, *J* = 6 Hz, 2H, Ar-H), 7.24 (m, 2H, Ar-H), 6.79 (d, *J* = 6 Hz, 2H, Ar-H), 5.63 (s, 1H, CH), 4.01 (q, *J* = 12 Hz, 4H, 2 x N-CH_2), 2.05 (q, *J* = 15 Hz,

4H 2 x CH_2), 3.72 (s, 3H, OCH_3), 1.01 (s, 6H, 2 x CH_3), 0.87 (s, 6H, 2 x CH_3); EI-MS: 558 $(M+Na)^+$;Anal. Calcd. For$C_{30}H_{33}N_9O$ (535.46):C, 67.27; H, 6.21; N, 23.53. Found: C, 62.03; H, 6.28, N, 23.29.

For **(4h)**: Mp = 262°C; IR (KBr, cm^{-1}): ν 2961, 2934, 1655, 1590, 1508, 1461, 1321, 1241, 1126, 780, 536; ^{1}HNMR (300 MHz, $CDCl_3$):δ 7.30 (d, J = 9 Hz, 2H, Ar-H), 7.09 (d, J = 9 Hz, 2H, Ar-H), 6.80 (s, 2H, Ar-H), 5.73 (s, 1H, CH), 4.06 (q, J = 9 Hz, 4H, 2 x N-CH_2), 3.79 (s, 9H, 3 x OCH_3), 2.45 (s, 3H, CH_3), 2.10 (q, J = 12 Hz, 4H, 2 x CH_2), 1.03 (s, 6H, 2 x CH_3), 0.88 (s, 6H, 2 x CH_3);EI-MS: 632 $(M+Na)^+$;Anal. Calcd. For$C_{33}H_{39}N_9O_3$ (609.32):C, 65.01; H, 6.45; N, 20.68. Found: C, 64.93; H, 6.38, N, 20.55.

CONCLUSION

In conclusion, a new green and efficient approach to 1,8-dioxo-decahydroacridines catalyzed by TCS under solvent-free conditions has been presented. The present method has several advantages from economical and environmental point of view, such as mild reaction conditions without use of any harmful organic solvent, cheap and easily handled reagent, and the easy purification of products. In addition, use of the prepared 1,8-dioxo-decahydroacridines in synthesis of novel aryl-pyrido-di-[3,2-c]tetrazolo[1,5-a]azepine derivatives by readily available TCS-NaN_3 was also presented. Biological evaluation of the novel functionalized pyrido-bistetrazoloazepines described in this work is currently in progress.

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