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Nano-$TiCl_4/SiO_2$: An efficient heterogeneous solid acid catalyst for the one pot cascade five-component synthesis of densely functionalized tetrahydropyridines

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Abstract. Nano-$TiCl_4/SiO_2$ was found to be an inexpensive and efficient heterogeneous solid acid catalyst for the synthesis of one-pot cascade synthesis of highly functionalized asymmetric tetrahydropyridines from the five-component condensation reaction of the *para*-substituted anilines and aromatic aldehydes with ethyl acetoacetate under thermal conditions. Novel methodology, environmentally benign conditions, clean protocol, easy work-up and high yields are the important advantages of this protocol. The products were characterized using physical and spectroscopic data such as FT-IR, ^{1}H-NMR and in some cases ^{13}C-NMR and CHN analysis.

Keywords. Tetrahydropyridines; Nano-$TiCl_4/SiO_2$; heterogeneous catalyst; five-component reaction; one-pot synthesis.

1. Introduction

Undoubtedly, heterocyclic chemistry forms the largest and the most diverse family of organic chemistry.[1] In particular, nitrogen-containing heterocyclic compounds have always played a key role in the pharmaceutical and agrochemical industries.[2] Numerous methods have been reported for the preparation of these compounds.[3] In this regard, multicomponent reactions (MCRs) as a powerful method have widely been used for manufacturing heterocyclic compounds with a variety and complexity of structures,[4] especially in the preparation of active pharmaceutical compounds.[5] On the other hand, MCRs have been demonstrated as a fixed method to access useful heterocycles with high selectivity and atom economy as well as procedural simplicity. MCRs have been used for the formation of carbon–carbon and carbon hetero atom bonds in a one-pot synthesis proceeding from simple available starting materials.[6] Protocols involved cascade and multicomponent reactions representing an interesting area of exploration. These reactions have been utilized for building complex molecules from readily available starting materials in few steps.[7]

In this context, tetrahydropyridines (THPs) and their derivatives are noteworthy as they possess potent pharmaceutical properties like anti-emetic and anti-psychotic[8], anti-cancer[9] and recently, as anti-malarial agents.[10] THPs have been used as drugs in the treatment of diseases such as Alzheimer (GTS-21)[11] and central nervous system (CNS) disorders (Ro10-5824) (figure 1).[12] Hence, in the last few years, the synthesis of these compounds had considerable interest. A number of methods have been reported for the synthesis of highly functionalized THPs.[13–17] These procedures suffer from some disadvantages such as excess of costly reagents and catalysts. Lately, the synthesis of these compounds have been developed using MCRs in the presence of $InCl_3$,[18] BDMS,[19] L-proline/TFA,[20] TBATB,[21] I_2,[22] CAN,[23] $ZrOCl_2{\cdot}8H_2O$,[24] $ZrCl_4$,[25] *p*-$TsOH{\cdot}H_2O$,[26] $Fe(NO_3)_3{\cdot}9H_2O$,[27] $FeCl_3/SiO_2$,[28] Amberlite IRA400-Cl resin/I_2/KI[29]. Previously, the stereochemistry of two stereogenic centres was determined using chiral phosphoric acids (CPAs).[30] However, some of these methods have disadvantages such as drastic reaction conditions against the principles of green chemistry. In recent times, utilization of the heterogeneous catalysts in organic synthesis as clean processes which result improvement of yield and selectivity of products.[31]

Titanium compounds are non-toxic, environment friendly, also mild and efficient Lewis acid catalysts used extensively in organic transformations.[32] Nano silica supported $TiCl_4$ is a mild heterogeneous solid acid which promotes acidic catalyzed organic reactions.[33]

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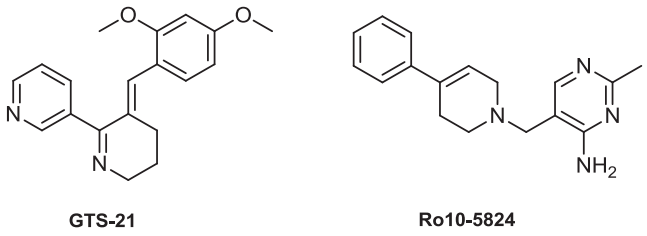
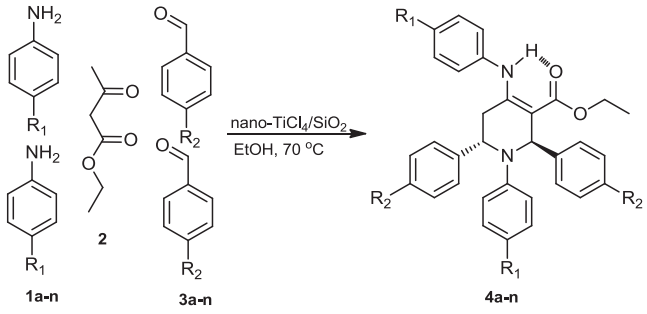


Figure 1. Chemical structure of two drugs of THP derivatives.



Scheme 1. Synthesis of THPs **4a-n** catalyzed by Nano-$TiCl_4/SiO_2$.

This catalyst does not need special precautions for preparation, handling or storage, and it can be stored at ambient temperature for months without losing its catalytic activity.

In continuation, we developed an eco-friendly approach for the synthesis of tetrahydropyridines **4a-n** *via* a five-component condensation reaction of the *para*-substituted anilines **1** with ethyl acetoacetate **2** and *para*-substituted benzaldehydes **3** in the presence of nano silica supported titanium tetrachloride (nano-$TiCl_4/SiO_2$) as an inexpensive and efficient solid acid catalyst in EtOH at 70°C (scheme 1).

2. Experimental

2.1 *Materials and instruments*

All chemicals and solvents were purchased from the Merck and Fluka Chemical Companies in high purity. Materials used were commercial reagent grade. FT-IR spectra were recorded as KBr pellet on a Magna Perkin-Elmer 550 Nicolet spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker DXR-400 Avance spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Elemental analysis CHN was performed using a Vario EL analyzer. The SEM and TEM of nano particles were determined with a VEGA/TESCAN scanning electron microscope and LEO912AB-OMEGA transmission electron microscopy, respectively. The thermal gravimetric analysis (TGA) was done with 'NETZSCH TG 209 F1 Iris' instrument. Melting points were obtained with a Yanagimoto micro melting point apparatus. The purity determination of the substrates and reactions monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

2.2 *Preparation of 50% $TiCl_4/SiO_2$ and 50% nano-$TiCl_4/SiO_2$*[33]

In a well-ventilated system, $TiCl_4$ (0.29 mL) was added dropwise to the mixture of silica gel or nano silica gel (0.5 g) in chloroform (5 mL). The mixture was stirred for one hour at room temperature. The resulted suspension was filtered, washed with chloroform and dried at room temperature.

2.3 *General procedure for synthesis of THPs **4a–n***

In a round-bottom flask equipped with a reflux condenser (50 mL), firstly a mixture of *para*-substituted aniline (**1**) (4 mmol) and ethyl acetoacetate (**2**) (2 mmol) in absolute ethanol (10 mL) was heated for 30 min in the presence of nano-$TiCl_4/SiO_2$ (0.10 g). Then, the *para*-substituted benzaldehyde (**3**) (4 mmol) was added in one portion and the mixture was heated at 70°C for appropriate time (table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was allowed to be cooled. Then, the mixture was filtered off, washed with EtOH (3×5 mL) and dried. Chloroform (10 mL) was added to remove the catalyst. The solvent was evaporated in air. The crude product was recrystallized from ethanol to give the corresponding THPs **4a–n** in high yields with high purification. The products were identified by physical and spectroscopic data.

2.4 *Spectroscopic data*

2.4a *Ethyl-1-phenyl-4-(phenylamino)-2,6-di-4-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate **4a***: Gray solid. M.p. 228–230°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3234, 3028, 2981, 2921, 2868, 1650, 1594, 1500, 1370, 1325, 1254, 1174, 1068, 748, 695. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.30 (s, 1H, NH), 7.23 (br. s, 2H, Ar–H), 7.1 (br. s, 11H, Ar–H), 6.68–6.51 (br. m, 3H, Ar–H), 6.42 (s, 1H, H-2), 6.31 (br. s, 2H, Ar-H), 5.13 (m, 1H, H-6), 4.47 (m, 1H, $O\underline{CH_2}CH_3$), 4.33 (m, 1H, $O\underline{CH_2}CH_3$), 2.86 (m, 1H, H-5), 2.79 (d, 1H, ^2J = 14.4 Hz, H-5′), 2.34 (s, 6H, Ar-$\underline{CH_3}$), 1.47 (t, J = 6 Hz, 3H, $OCH_2\underline{CH_3}$).

2.4b *Ethyl-1-phenyl-4-(phenylamino)-2,6-bis(4-chloropenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4b***: Gray solid. M.p. 202–204°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3236, 3058, 2981, 2869, 1653, 1594, 1495, 1368, 1323, 1255, 1068, 747, 694. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.30 (s, 1H, NH), 7.16–7 (m, 12H, Ar–H), 6.66 (br. s, 1H, Ar–H), 6.6–5.8 (m, 6H, Ar–H, H-2), 5.10 (m, 1H, H-6), 4.45 (m, 1H, O$\underline{CH_2}CH_3$), 4.33 (m, 1H, O$\underline{CH_2}CH_3$), 2.9–2.7 (m, 2H, H-5,5′), 1.32 (br. s, 3H, $OCH_2\underline{CH_3}$).

2.4c *Ethyl-1-phenyl-4-(phenylamino)-2,6-bis(4-bromophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4c***: Pale yellow solid. M.p. 218–220°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3238, 3033, 2979, 1652, 1595, 1496, 1323, 1252, 1068, 747, 694. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.29 (s, 1H, NH), 7.4 (br. s, 4H, Ar–H), 7.26–7.12 (m, 5H, Ar–H), 7.09 (br. s, 2H, Ar–H), 7.01 (br. s, 2H, Ar–H), 6.66 (br. s, 1H, Ar-H), 6.52–6.38 (m, 4H, Ar-H), 6.34 (br. s, 1H, H-2), 5.08 (m, 1H, H-6), 4.44 (m, 1H, O$\underline{CH_2}CH_3$), 4.33 (m, 1H, O$\underline{CH_2}CH_3$), 2.83 (d, 1H, ^2J = 15.2 Hz, H-5), 2.75 (d, 1H, ^2J = 14.4 Hz, H-5′), 1.45 (br. s, 3H, $OCH_2\underline{CH_3}$).

2.4d *Ethyl-1-(4-tolyl)-4-(4-tolylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-arboxylate* ***4d***: Cream solid. M.p. 193–194°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3238, 3023, 2920, 1650, 1596, 1515, 1449, 1371, 1316, 1251, 1071, 700. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.22 (s, 1H, NH), 7.48–7.27 (m, 8H, Ar–H), 7.21 (m, 2H, Ar–H), 7.08–6.85 (br. s, 4H, Ar–H), 6.62–6.42 (br. d, 3H, J = 8.4 Hz, Ar–H, H-2), 6.29-6.16 (d, 2H, J = 7.6 Hz, Ar–H), 5.12 (m, 1H, H-6), 4.45 (m, 1H, O$\underline{CH_2}CH_3$), 4.33 (m, 1H, O$\underline{CH_2}CH_3$), 2.85 (dd, 1H, ^2J = 15 Hz, J = 5.6 Hz, H-5), 2.74 (d, 1H, ^2J = 15 Hz, H-5′), 2.26 (s, 3H, Ar-$\underline{CH_3}$), 2.16 (s, 3H, Ar-$\underline{CH_3}$), 1.46 (t, 3H, J = 6.8 Hz, $OCH_2\underline{CH_3}$).

2.4e *Ethyl-1,2,6-tri-4-tolyl-4-(4-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4e***: Cream solid. M.p. 170–172°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3237, 3023, 2979, 2919, 1651, 1598, 1514, 1448, 1370, 1321, 1253, 1176, 1070, 795. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.22 (s, 1H, NH), 7.22 (d, 2H, J = 7.2 Hz, Ar–H), 7.08 (d, 6H, J = 6.4 Hz, Ar–H), 6.89 (d, 4H, J = 5.6 Hz, Ar–H), 6.43 (d, 2H, J = 8 Hz, Ar–H), 6.37 (s, 1H, H-2), 6.16 (d, 2H, J = 7.2 Hz, Ar–H), 5.09 (m, 1H, H-6), 4.44 (m, 1H, O$\underline{CH_2}CH_3$), 4.33 (m, 1H, O$\underline{CH_2}$CH3), 2.82 (dd, 1H, ^2J = 15 Hz, J = 5.6 Hz, H-5), 2.73 (d, 1H, ^2J = 15 Hz, H-5′), 2.34 (s, 3H, Ar-$\underline{CH_3}$), 2.32 (s, 3H, Ar-$\underline{CH_3}$), 2.24 (s, 3H, Ar-$\underline{CH_3}$), 2.15 (s, 3H, Ar-$\underline{CH_3}$), 1.45 (t, 3H, J = 6.8 Hz, $OCH_2\underline{CH_3}$).

2.4f *Ethyl-1-(4-tolyl)-4-(4-tolylamino)-2,6-bis(4-bromophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4f***: Pale yellow solid. M.p. 215–217°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3238, 2976, 2918, 2859, 1651, 1597, 1515, 1483, 1313, 1251, 1069, 1009, 795. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.21 (s, 1H, NH), 7.39 (d, 4H, J = 7.6 Hz, Ar–H), 7.19 (d, 2H,J = 7.6 Hz, Ar–H), 7.00 (d, 2H, J = 7.6 Hz, Ar–H), 6.96 (d, 2H, J = 7.6 Hz, Ar–H), 6.89 (d, 2H, J = 7.6 Hz, Ar–H), 6.36 (d, 1H, J = 7.6 Hz, Ar–H), 6.30 (s, 1H, H-2), 6.29 (d, 2H, J = 7.6 Hz Ar–H), 5.04 (m, 1H, H-6), 4.44 (br. d, 1H, O$\underline{CH_2}CH_3$), 4.33 (br. d, 1H, O$\underline{CH_2}CH_3$), 2.78 (dd, 1H, ^2J = 14.4 Hz, J = 5.2 Hz, H-5), 2.71 (d, 1H, ^2J = 15.2 Hz, H-5′), 2.29 (s, 3H, Ar-$\underline{CH_3}$), 2.18 (s, 3H, Ar-$\underline{CH_3}$), 1.44 (t, 3H, J = 6.4Hz, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz)/δ ppm: 168.0, 156.1, 144.3, 143.3, 141.8, 141.9, 135.9, 135.0, 131.7, 131.3, 129.6, 128.5, 128.2, 125.88, 125.82, 120.8, 120.1, 113.0, 97.2, 59.7, 57.4, 54.9, 33.6, 20.9, 20.2, 14.8. Anal. Calcd for $C_{34}H_{32}Br_2N_2O_2$: C, 62.87; H, 4.80; N, 4.44. Found: C, 59.68; H, 4.74; N, 4.13.

2.4g *Ethyl-1-(4-ethylphenyl)-4-((4-ethylphenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4g***: Cream solid. M.p. 187–189°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3238, 2963, 1652, 1599, 1515, 1451, 1373, 1315, 1250, 1069, 700. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.23 (s, 1H, NH), 7.35 (d, 3H, J = 7.2 Hz, Ar–H), 7.31–7.26 (m, 5H, Ar–H), 7.21 (t, 2H, J = 7.2 Hz, Ar–H), 6.91 (d, 4H, J = 7.2 Hz, Ar–H), 6.46 (d, 2H, J = 8.8 Hz, Ar–H), 6.44 (s, 1H, H-2), 6.17 (d, 2H, J = 7.2 Hz, Ar–H), 5.14 (m, 1H, H-6), 4.46 (m, 1H, O$\underline{CH_2}CH_3$), 4.33 (m, 1H, O$\underline{CH_2}CH_3$), 2.85 (dd, 1H, ^2J = 15.2 Hz, J = 5.6 Hz, H-5), 2.75 (d, 1H, ^2J = 15.2Hz, H-5′), 2.56 (q, 2H, J = 7.5 Hz, Ar-$\underline{CH_2}$), 2.47 (q, 2H, J = 7.3 Hz, Ar-$\underline{CH_2}$), 1.47 (t, 3H, J = 7.6 Hz, $OCH_2\underline{CH_3}$), 1.18 (t, 3H, J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$), 1.12 (t, 3H, J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$);^{13}C NMR ($CDCl_3$, 100 MHz)/δ ppm: 168.3, 156.5, 145.1, 144.5, 143.2, 141.9, 135.5, 131.6, 128.6, 128.2, 127.1, 126.7, 126.5, 126.2,126.0, 112.9, 97.8, 59.6, 58.4, 55.3, 33.6, 28.3, 27.6, 15.7, 15.5, 14.9. Anal. Calcd for $C_{36}H_{38}N_2O_2$: C, 81.47; H, 7.22; N, 5.28. Found: C, 78.03; H, 6.96; N, 5.10.

2.4h *Ethyl-1-(4-ethylphenyl)-4-((4-ethylphenyl)amino)-2,6-di-4-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4h***: Cream solid. M.p. 176–178°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3231, 3020, 2967, 2925, 2865, 1650, 1601, 1514, 1452,

1369, 1320, 1255, 1177, 1070, 810. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.22 (s, 1H, NH), 7.23 (d, 2H, J = 7.6 Hz, Ar–H), 7.08 (m, 6H, Ar–H), 6.92–6.89 (m, 4H, Ar–H), 6.46 (d, 2H, J = 8.4 Hz, Ar–H), 6.38 (s, 1H, H-2), 6.19 (d, 2H, J = 7.6 Hz, Ar–H), 5.09 (m, 1H, H-6), 4.44 (m, 1H, O$\underline{CH_2}CH_3$), 4.30 (m, 1H, O$\underline{CH_2}CH_3$), 2.83 (dd, 1H, ^2J =14.8 Hz, J = 5.2 Hz, H-5), 2.74 (d, 1H, ^2J =14.8 Hz, H-5′), 2.56 (q, 2H, J = 7.2 Hz, Ar-$\underline{CH_2}$), 2.46 (q, 2H, J = 7.2 Hz, Ar-$\underline{CH_2}$), 2.35 (s, 3H, Ar-$\underline{CH_3}$), 2.32 (s, 3H, Ar-$\underline{CH_3}$), 1.45 (t, 3H, J = 6.8 Hz, $OCH_2\underline{CH_3}$), 1.18 (t, 3H, J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$), 1.12 (t, 3H, J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz)/δ ppm: 168.3, 156.4, 145.2, 141.7, 141.5, 140.1, 136.4, 135.6, 135.5, 131.3, 129.2, 128.8, 128.1, 126.6, 126.4, 125.9, 112.8, 97.9, 59.5, 58.0, 55.0, 33.6, 28.2, 21.1, 21.0, 15.6, 15.4, 14.8. Anal. Calcd for $C_{38}H_{42}N_2O_2$: C, 81.68; H, 7.58; N, 5.01. Found: C, 76.92; H, 7.37; N, 4.73.

2.4i *Ethyl-1-(4-ethylphenyl)-4-((4-ethylphenyl)amino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4i***: White solid. M.p. 209–211°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3234, 2967, 1650, 1603, 1514, 1485, 1405, 1368, 1316, 1252, 1068, 813. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.23 (s, 1H, NH), 7.26 (s, 3H, Ar–H), 7.08 (d, 3H, J = 7.6 Hz, Ar–H), 6.98 (d, 3H, J = 7.6 Hz, Ar–H), 6.92 (d, 2H, J = 7.6 Hz, Ar–H), 6.5–6.3 (m, 6H, Ar–H, H-2), 5.07 (m, 1H, H-6), 4.43 (m, 1H, O$\underline{CH_2}CH_3$), 4.35 (m, 1H, O$\underline{CH_2}CH_3$), 2.79 (dd, 1H, ^2J = 14.4 Hz, J = 5.2 Hz, H-5), 2.74 (d, 1H, ^2J = 14.8 Hz, H-5′), 2.59 (q, 2H, J = 7.5 Hz, Ar-$\underline{CH_2}CH_3$), 2.49 (q, 2H, J = 7.6 Hz, Ar-$\underline{CH_2}CH_3$), 1.45 (t, 3H, J = 6.8 Hz, $OCH_2\underline{CH_3}$), 1.20 (t, 3H, J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$), 1.14 (t, 3H, J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz)/δ ppm: 168.1, 156.2, 144.6, 142.9, 142.2, 141.3, 135.2, 132.8, 132.2, 132.1,128.4, 128.1, 127.9, 125.9, 113.1, 97.3, 59.7, 57.5, 54.9, 33.7, 28.3, 27.6, 15.7, 15.5, 14.8. Anal. Calcd for $C_{36}H_{36}Cl_2N_2O_2$: C, 72.11; H, 6.05; N, 4.67. Found: C, 70.95; H, 6.38; N, 4.58.

2.4j *Ethyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4j***: Pale yellow solid, M.p. 202–204°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3242, 2975, 1647, 1600, 1495, 1451, 1372, 1320, 1254, 1071, 803, 729, 697. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.25 (s, 1H, NH), 7.31–7.23 (m, 8H, Ar–H), 7.17 (d, 2H, J = 7.2 Hz, Ar–H), 7.06 (d, 2H, J = 8.4 Hz, Ar–H), 7.01 (d, 2H, J = 8.4 Hz, Ar–H), 6.44 (d, 2H, J = 8.6 Hz, Ar–H), 6.40 (s, 1H, H-2), 6.18 (d, 2H, J = 8.6 Hz, Ar–H), 5.11 (d, J = 4.4 Hz,1H, H-6), 4.49 (m, 1H, O$\underline{CH_2}CH_3$), 4.35 (m, 1H, O$\underline{CH_2}CH_3$), 2.86 (dd, 1H, ^2J =15.2 Hz, J = 5.6 Hz, H-5), 2.71 (d, 1H, ^2J = 15.2 Hz, H-5′), 1.46 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$).

2.4k *Ethyl-1,2,6-tris(4-chlorophenyl)-4-((4-chlorophenyl) amino)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4k***: White solid. M.p. 214–215°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3435, 3236, 2979, 1652, 1603, 1493, 1318, 1251, 1093, 1069, 802. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.24 (s, 1H, NH), 7.23–7.02 (m, 12H, Ar–H), 6.33 (s, 5H, Ar–H, H-2), 5.04 (s, 1H, H-6), 4.43 (br. s, 1H, O$\underline{CH_2}CH_3$), 4.32 (br. s, 1H, O$\underline{CH_2}CH_3$),2.79 (br, s, 1H, H-5), 2.69 (br. s, 1H, H-5′), 1.44 (br, s, 3H, $OCH_2\underline{CH_3}$).

2.4l *Ethyl-1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4l***: Pale yellow solid. M.p. 200–202°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3240, 2975, 1648, 1602, 1450, 1372, 1319, 1253, 1068, 1010, 800, 700. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.25 (s, 1H, NH), 7.29 (br. s, 8H, Ar–H), 7.20 (d, 2H, J = 8.0 Hz, Ar–H), 7.16 (d, 2H, J = 8.4 Hz, Ar–H), 7.14 (d, 2H, J = 8.4 Hz, Ar–H), 6.40 (d, 2H, J = 7.2 Hz, Ar–H), 6.39 (s, 1H, H-2), 6.11 (d, 2H, J = 8.0 Hz, Ar–H), 5.11 (d, 1H, J = 4.4 Hz, H-6), 4.48 (m, 1H, ^2J = 10.8 Hz,J = 7.2 Hz, O$\underline{CH_2}CH_3$), 4.35 (m, 1H, ^2J = 10.8 Hz,^{J} = 7.2 Hz, O$\underline{CH_2}CH_3$), 2.86 (dd, 1H, ^2J = 14.8 Hz, J = 6.0 Hz, H-5), 2.71 (d, 1H, ^2J = 14.8 Hz, H-5′), 1.48 (t, 3H, J = 7.2 Hz, $OCH_2\underline{CH_3}$).

2.4m *Ethyl-1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4m***: Cream solid. M.p. 193–195°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3234, 2981, 1651, 1609, 1491, 1404, 1369, 1321, 1252, 1176, 1068, 1010, 804, 755. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.25 (s, 1H, NH), 7.27–7.16 (m, 6H, Ar–H), 7.05 (s, 3H, Ar–H), 6.33–6.28 (m, 8H, Ar–H, H-2), 5.06 (m, 1H, H-6), 4.46 (br. s,, 1H, O$\underline{CH_2}CH_3$), 4.34 (br. s, 1H, O$\underline{CH_2}CH_3$), 2.81 (br. s, 1H, H-5), 2.66 (d, 1H, ^2J = 15.2 Hz, H-5′), 1.46 (s, 3H, $OCH_2\underline{CH_3}$).

2.4n *Ethyl-1-(4-bromophenyl)-4-((4-bromophenyl) amino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* ***4n***: White solid. M.p. 217–219°C. IR (KBr)/$\bar{\upsilon}$ (cm^{-1}): 3234, 2931, 2918, 2834, 1650, 1608, 1499, 1319, 1249, 1173, 1068, 802. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 10.25 (s, 1H, NH), 7.22 (d, 2H, J = 8 Hz, Ar–H), 7.18 (d, 2H, J = 8.4 Hz, Ar–H), 7.13 (d, 2H, J = 8.8 Hz, Ar–H), 7.04 (d, 2H, J = 8 Hz, Ar–H), 6.95–6.78 (br, s, 4H, Ar–H), 6.39 (d, 2H,

J = 8.4 Hz, Ar–H), 6.29 (s, 1H, H-2), 6.19 (d, 2H, J = 8 Hz, Ar–H), 5.04 (m, 1H, H-6), 4.46 (br. s, 1H, $O\underline{CH_2}CH_3$), 4.34 (br. s, 1H, $O\underline{CH_2}CH_3$), 3.78 (s, 6H, OMe), 2.83 (br. d, 2H, ^2J = 14.8 Hz, H-5), 2.69 (d, 1H, ^2J = 14.8 Hz, H-5′), 1.46 (t, 3H, J = 6.8 Hz, $OCH_2\underline{CH_3}$).

3. Results and Discussions

3.1 *Characterization of the catalyst*

For the present work, the catalyst nano silica supported titanium tetrachloride (nano-$TiCl_4/SiO_2$), was prepared *via* the reaction of nano SiO_2 with $TiCl_4$. The characteristics of nano-$TiCl_4/SiO_2$ was studied by FT-IR, Powder X-ray diffraction (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM).[33] The particle size in the TEM photograph were calculated to be between 14–20 nm. Thermal stability of nano-$TiCl_4/SiO_2$ was studied by Thermal gravimetric analysis (TG-DTG) (figure 2). TG-DTG pattern of the catalyst was detected in the range of 23.43 to 513.43°C The catalyst is stable to 173.43°C and only 2.98% of its weight was decreased in 173.43°C This initial reduced mass (2.98%) of catalyst is related to removal of catalyst moisture. From 173°C to 513°C, the weight loss of the catalyst is 2.15%. Only 5.13% of the catalyst weight was reduced between 23.43 to 513.43°C.

3.2 *The optimization of reaction conditions*

The synthesis of THPs is typically an intermolecular nucleophilic addition reaction (Mannich reaction type) which is involved several intermediates. In order to optimize the solvent and temperature to achieve the highest yield, the model reaction of 4-chloroaniline with ethyl acetoacetate and benzaldehyde for preparation of THP **4j** was carried out in the presence of 0.1 g of $TiCl_4/SiO_2$ and at diverse temperature conditions using various solvents. The results are indicated in table 1, entries 1–14. As shown in this table, it was remarkably enhanced in the yield of reaction in ethanol at 70°C with shorter time (entry 14).

In continuation of this work, in order to use the optimum amount of the catalyst for all reactions and to attain higher yield of the product, the mentioned model reaction was surveyed with different amounts of $TiCl_4/SiO_2$. The obtained results are summarized in table 1, entries 15–18. As can be seen in this table, the optimum amount of the used $TiCl_4/SiO_2$ was 0.15 g (entry 16). Nano-$TiCl_4/SiO_2$ in comparison with $TiCl_4/SiO_2$ was showed higher yields at the shorter time using the different amount of related catalyst, entries 18–20. As shown in table 1, the optimum amount of the utilized nano-$TiCl_4/SiO_2$ was 0.10 g (entry 19) included the optimized condition of the preparation of THP **4j**. The reusability of nano catalyst at 70°C was tested (table 1, entries 21, 22). The catalyst residue in the preparation of THP **4j** was washed with chloroform, dried at room temperature and reused. A considerable decrease was noticed in catalysis activity.

The achieved results of the synthesis of the THP derivatives **4a**–**n** from the reaction of various *para*-substituted anilines **1a**–**n** and ethyl acetoacetate **2** with *para*-substituted benzaldehydes **3a**–**n** in the presence of nano-$TiCl_4/SiO_2$ in EtOH at 70°C are shown in table 2.

An investigation was carried out on the usage of various substituents on the phenyl rings of benzaldehyde and aniline. The preparation reaction of THPs with electron-donating groups such as alkyl and halogen on the phenyl ring of benzaldehyde as well as aniline successfully occurred. Phenyl rings containing electron-drawing groups as nitro substituents did not yield even

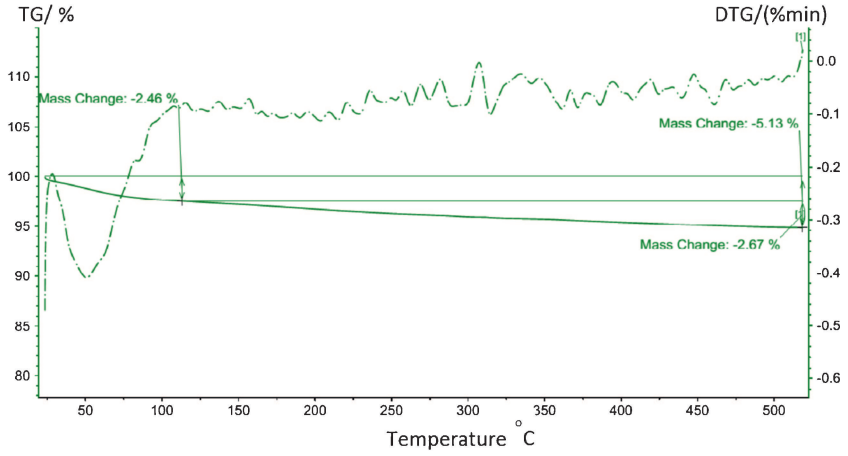
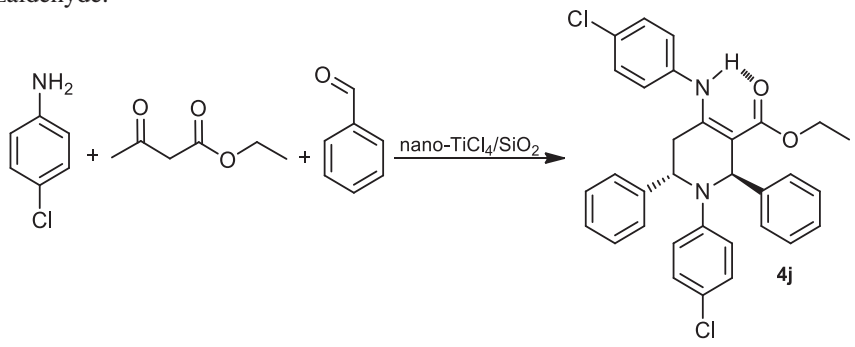


Figure 2. TG-DTG pattern of nano-$TiCl_4/SiO_2$.

Table 1. The optimization of the reaction parameters on the nano-$TiCl_4/SiO_2$ catalysed model reaction for the synthesis of **4j** between 4-chloroaniline with ethyl acetoacetate and benzaldehyde.[a]



Entry	Solvent	Catalyst (g)	Condition	Time (h)	Yield (%)[b]
1	Neat	$TiCl_4/SiO_2$ (0.05)	r.t.	30	25
2	Neat	$TiCl_4/SiO_2$ (0.1)	r.t.	24	30
3	Neat	$TiCl_4/SiO_2$(0.1)	70°C	20	35
4	Neat	$TiCl_4/SiO_2$ (0.1)	100°C	17	38
5	$CHCl_3$	$TiCl_4/SiO_2$(0.1)	r.t.	18	40
6	$CHCl_3$	$TiCl_4/SiO_2$(0.1)	reflux	13	40
7	THF	$TiCl_4/SiO_2$ (0.1)	r.t.	20	44
8	THF	$TiCl_4/SiO_2$ (0.1)	reflux	13	45
9	CH_3CN	$TiCl_4/SiO_2$ (0.1)	r.t.	20	46
10	CH_3CN	$TiCl_4/SiO_2$ (0.1)	reflux	11	53
11	CH_3OH	$TiCl_4/SiO_2$ (0.1)	r.t.	17	50
12	CH_3OH	$TiCl_4/SiO_2$ (0.1)	60°C	12	59
13	C_2H_5OH	$TiCl_4/SiO_2$ (0.1)	r.t.	20	60
14	C_2H_5OH	$TiCl_4/SiO_2$ (0.1)	70°C	11	65
15	C_2H_5OH	$TiCl_4/SiO_2$ (0.13)	70°C	10	67
16	C_2H_5OH	$TiCl_4/SiO_2$ (0.15)	70°C	10	72
17	C_2H_5OH	$TiCl_4/SiO_2$ (0.18)	70°C	10	69
18	C_2H_5OH	Nano-$TiCl_4/SiO_2$ (0.05)	70°C	10	70
19	**C_2H_5 OH**	**Nano-$TiCl_4/SiO_2$(0.1)**	70°**C**	**7**	**81**
20	C_2H_5OH	Nano-$TiCl_4/SiO_2$ (0.13)	70°C	7	77
21	C_2H_5OH	Nano-$TiCl_4/SiO_2$ (0.1), 2ndrun	70°C	9	68
22	C_2H_5OH	Nano-$TiCl_4/SiO_2$ (0.1), 3rdrun	70°C	11	56

[a]Experimental conditions: 4-chloroaniline (4 mmol), ethyl acetoacetate (2 mmol) and benzaldehyde (4 mmol). [b]Isolated yield.

after prolonged reaction times. For example, the treatment of aniline (4 mmol) and 4-nitrobenzaldehyde (4 mmol) with ethyl acetoacetate (2 mmol) in the presence of nano-$TiCl_4/SiO_2$ (0.10 g) failed to give the corresponding THP even after 24 h. The reaction of 4-nitroaniline (4 mmol) and benzaldehyde (4 mmol) with ethyl acetoacetate (2 mmol) under the same reaction conditions did not give any product even after 30 h. Ultimately, when a mixture of 4-methyaniline (4 mmol) and 4-nitrobenzaldehyde (4 mmol) with ethyl acetoacetate (2 mmol) was treated under similar conditions for 48 h, the corresponding THP was not formed.

3.3 *Comparision of nano-$TiCl_4/SiO_2$ with other catalysts*

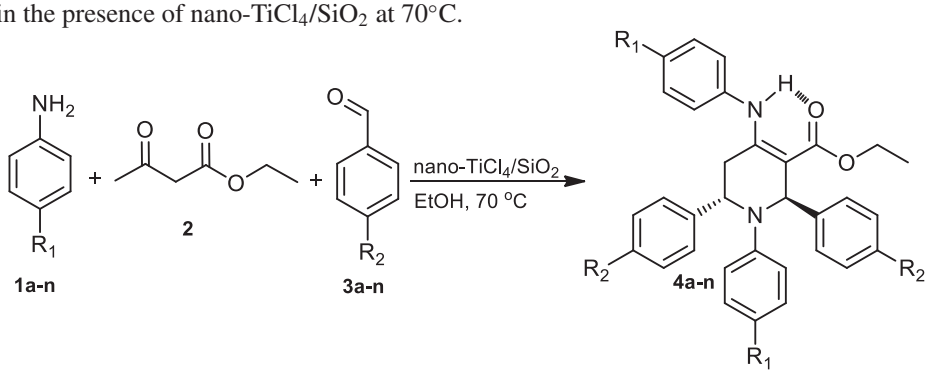
A comparison between this work with some previous reported methods for the synthesis of **4j** is shown in table 3. As can be shown in this table, except of AcOH, with nano-$TiCl_4/SiO_2$ achieved higher yield at the shorter reaction time using of EtOH over 70°C in the presence of 0.10 g catalyst.

A reasonable mechanism for these conversions has been presented in the previous methods.[22,26,28,29]

3.4 *The spectroscopic study of THPs*

The structure of the THPs is assigned by physical and spectroscopic data (M.p., FT-IR, ^{1}H NMR) and the new products of **4f–i**, besides the mentioned methods characterized by ^{13}C NMR spectroscopy and C.H.N. analysis. The relative stereochemistry of THPs was confirmed by single-crystal X-ray crystallography in the previous literatures.[22,30,35,37] In the FT-IR spectra, as shown in figure 3 for the THP **4g**, the conjugated C=O

Table 2. The results of the reaction of various *para*-sustituted anilines, **1a-n** and ethyl acetoacetate **2** with *para*-sustituted benzaldehydes, **3a-n** in the presence of nano-$TiCl_4/SiO_2$ at 70°C.



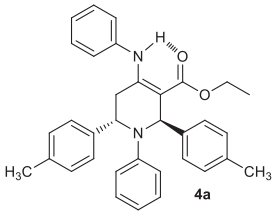
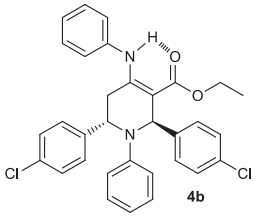
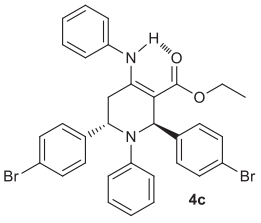
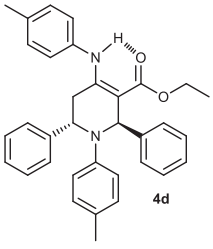
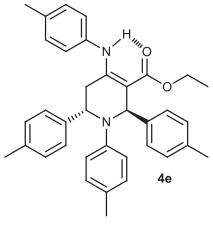
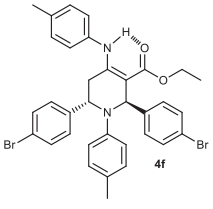
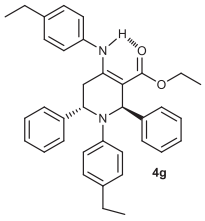
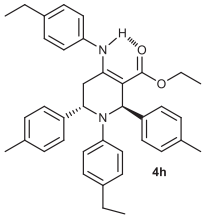
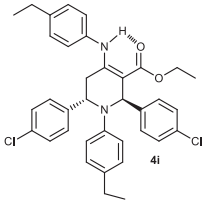
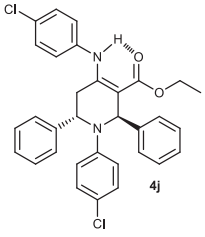
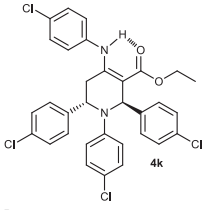
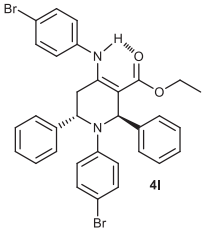
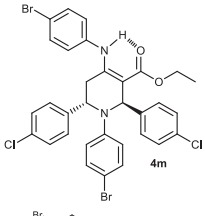
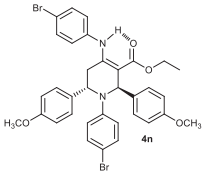
Entry	R1	R2	THP	Time (h)	Yield (%)[a]	M.p. (lit. report)[Refb]
1	H	Me		8	72	228-230 (226-228)[29]
2	H	Cl		8	70	202-204[34c]
3	H	Br		7	74	218-220[34c]
4	Me	H		7	78	193-194 (194-196)[27]
5	Me	Me		8	80	170-172 (169-171)[27]
6	Me	Br		8	80	215-217[d]

Table 2. (Continued)

7	Et	H		7	74	187-189[d]
8	Et	Me		8	79	176-178[d]
9	Et	Cl		8	78	209-211[d]
10	Cl	H		7	81	202-204 (198-201)[26]
11	Cl	Cl		9	80	214-215[28c]
12	Br	H		7	78	200-202 (197-199)[27]
13	Br	Cl		9	77	193-195[34c]
14	Br	OMe		7	80	217-219 (216-218)[29]

[a]Isolated yields. [b]The references of known products in the literature. [c]No reported. [d]New product.

Table 3. Comparison of the efficiency of nano-$TiCl_4/SiO_2$ with some of the reported procedures on the preparation of **4j** using of 4-chloroaniline (2 mmol), benzaldehyde (2 mmol) with ethylacetoacetate (1 mmol) in EtOH at 70°C.

Catalyst	Conditions	Time (h)	Yield (%)[a]	Ref
AcOH (5 mL)	AcOH/ r.t.	1	92	35
CAN (0.15 mol)	MeCN/ r.t.	35	68	23
p-TsOH.H_2O (0.11 g)	EtOH/ r.t.	12	88	26
SSA (0.1 g)	EtOH/60°C	9	78	36
L-proline/TFA (20 mol%)	AcCN/ 20–30°C	22	75	20
Nano-$TiCl_4/SiO_2$(0.10 g)	**EtOH/70°C**	**7**	**81**	**This work[b]**

[a]Isolated yields. [a]Experimental conditions: 4-chloroaniline (4 mmol), ethyl acetoacetate (2 mmol) and benzaldehyde (4 mmol).

stretching frequency appeared around 1650 cm^{-1} as an index strong peak. The C=C stretching frequency of aromatic rings paired in the range 1448–1485 cm^{-1} and one's in the region 1594–1610 cm^{-1} with sharp absorptions. C-O ester as one of the strongest of absorptions noticed about 1250 cm^{-1}. The formation signal of N-H was very weak at 3231–3242 cm^{-1} (figure 3). The expansion of assigned hydrogen signals in the ^{1}H NMR spectrum of THP **4j** and The stereochemistry of THPs structure are shown in figures 4 and 5. In the ^{1}H NMR spectrum, the distinct peak near δ 10.5 ppm is assigned to the proton of secondary amine as hydrogen bonding and resonance with C=O bond was deshielded (figure 4). Diastereotopic hydrogens, H5 and H5′ located on the carbon atom (C5) adjacent to the stereocentre (C6) appeared near δ 2.9 (H5) and δ 2.7 (H5') ppm in doublet of doublets by splitting *via* geminal (H5') and *cis*-vicinal (H6) protons coupling ($^2J_{5'5}$ = 15.2, $^3J_{65}$ =5.6 Hz) and in doublet by splitting *via* geminal (H5) proton coupling ($^2J_{55'}$ =15.2), respectively (figures 4 and 5).[38] As shown, the splitting of *trans*-vicinal (H6) and H5' protons was not observed ($^3J_{65'}$ =0 Hz). The hydrogen of chiral centre (H6) nearby diastereotopic hydrogens was noticed around δ 5.1 ppm in a weak doublet ($^3J_{56}$ =5.6 Hz). As mentioned, only by splitting *via cis*-vicinal (H5) proton (figures 4 and 5). The other hydrogen of stereocenter (H2) was seen at about δ 6.4 ppm in a singlet (figure 4). Two hydrogens ($O\underline{CH_2}CH_3$), as diastereotopic hydrogens appeared near δ 4.4 ppm in multiplets by splitting *via* the geminal and vicinal protons coupling as doublet of quartets (figure 4). Finally, the hydrogens of methyl ($OCH_2\underline{CH_3}$) are assigned as a triplet at δ 1.5 ppm (figure 4). In the ^{13}C NMR spectra, the index signal about δ 169 ppm is assigned to the ester C=O bond. The signals about δ 35 and δ 55 ppm are assigned to the carbons 5 and 6. The signals at around δ 58 ppm and δ 60 ppm are assigned to the carbon atoms of OCH_2 and

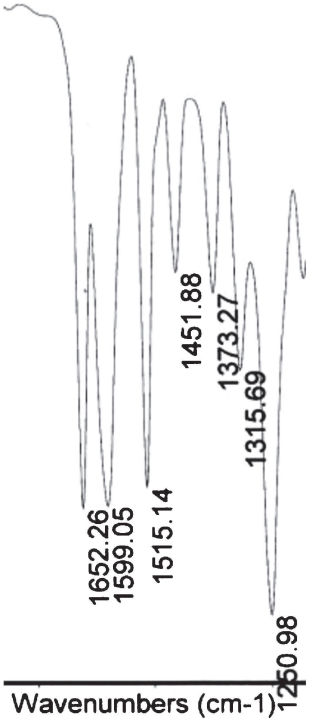


Figure 3. The observed sharp peaks in the IR spectrum of THP **4g**.

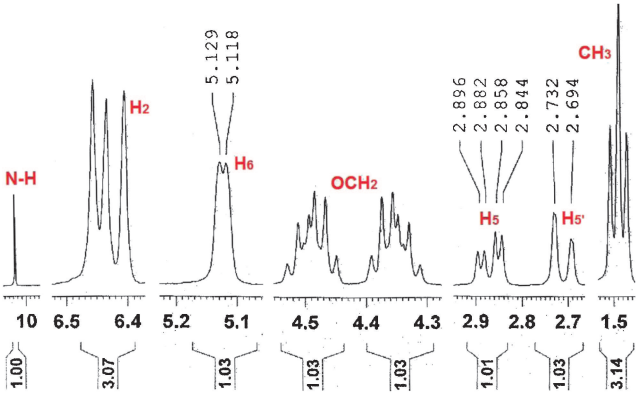


Figure 4. Expansion some of the assigned hydrogens in the ^{1}H spectrum of THP **4j**.

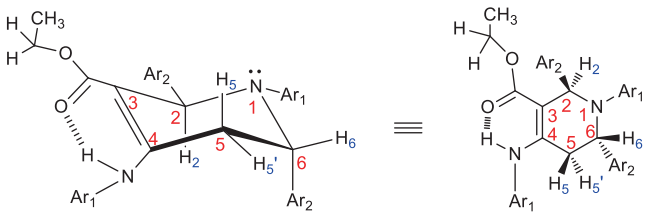


Figure 5. The proposed structure for THPs using X-ray pattern and coupling constant in ^{1}H NMR.

C2. The carbon atoms of linked to C=O (C3) and C4 are assigned around δ 98 and δ 155 ppm, respectively.

4. Conclusions

An efficient MCR protocol for the preparation of densely functionalized asymmetrical tetrahydropyridines catalyzed by titanium tetrachloride supported on nano silica from various *para*-substituted anilines and benzaldehydes with ethyl acetoacetate has been developed. The reaction has been carried out in a one-pot cascade synthesis in the presence of nano-$TiCl_4/SiO_2$ as a solid acid supported catalyst under thermal conditions.

Supplementary Information

FT-IR and ^{1}H NMR spectra all of the compounds and ^{13}C NMR and CHN data of new compounds **4f**, **4g**, **4h** and **4i** are given in the supporting information. The electronic supporting information can be seen at http://www.ias.ac.in/chemsci/index.html.

Acknowledgements

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