ISSN: 0976-3376

Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

Asian Journal of Science and Technology
Vol. 08, Issue, 10, pp.6015-6021, October, 2017

RESEARCH ARTICLE

AN EFFICIENT DOMINO ONE-POT, FOUR-COMPONENT GREEN CHEMICAL APPROACH FOR THE SYNTHESIS OF STRUCTURALLY DIVERSE DIHYDROPYRIDINE FUSED MEDICINALLY PRIVILEGED HETEROSYSTEMS

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ARTICLE INFO

Article History:
Received 22nd July, 2017
Received in revised form
04th August, 2017
Accepted 28th September, 2017
Published online 09th October, 2017

Key words:
Multicomponent reactions,
2,3-quinolinedicarboxylate,
Pyrido-[2,3-d]-pyrimidine;
Pyrano[4,3-b] Pyridine,
Chromeno[4,3-b]pyridine.

ABSTRACT

The derivatives of structurally diverse dihydropyridine fused hetrocycles; 2,3-quinolinedicarboxylate,chromeno[4,3-b]pyridine-2,3-dicarboxylate, pyrido[2,3-d]pyrimidine-6,7-dicarboxylate, pyrano[4,3-b]pyridine-2,3-dicarboxylate incorporating medicinally privileged fused heterosystems have been synthesized by an environmentally benign, efficient and convenient synthesis involving the Iron(III)chloride-catalyzed four-component domino reaction of aromatic aldehydes, acetylenedicarboxylate and arylamines with cyclic 1,3- dicarbonyl compound in an ethanol medium. The selective formation of the very different pyridine fused heterocyclic derivatives depends on the structure of cyclic 1, 3-dicarbonyl compound.

INTRODUCTION

Due to their exceptional synthetic efficiency, environmental and economically positive implications, Multicomponent reactions (MCRs) have been proven to be a very elegant and rapid way to access complex molecular structures in a single synthetic operation from simple and easily available precursors with high atom economy and already become a useful synthetic tool in modern organic and medicinal chemistry.(Chandrasekhar, D. B. *et al*, 2017; Chen, Y.H. *et al*, 2017; Wang, H. *et al*, 2017; Rai, S. *et al*, 2017). One of the most important goals in organic and medicinal chemistry is the design and synthesis of molecules that have value as therapeutic agents. In this regard, heterocyclic compounds have proven to be versatile support structures that offer a high degree of structural diversity (Weiner, D. A., 1988). Fused heterocyclic scaffolds with nitrogen and oxygen atoms are fundamental to the medicinal chemistry for the development of several new drugs. Pyridines are ubiquitous in nature and its derivatives play a vital role in synthetic and medicinal chemistry (Altaf, A.A. *et al*, 2015).

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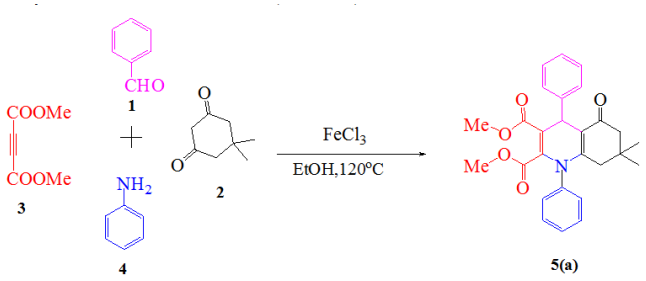
A large number of heterocyclic compounds containing pyridine rings have been reported for variety of biological activities such as antimicrobial (Patel, N.B. *et al*, 2011), anticancer(Srivastava, A. *et al*, 2011), anti diabetic (Firke, S. *et al*, 2009), anticonvulsant (Paronikyan, E.G. *et al,* 2002), antiviral (Bernardino, A. M. R. *et al*, 2007), Anti-Amoebic Agents (Bharti, N. *et al*, 2000) anti-HlV(Tucker, T. J. *et al*, 2008), antifungal and antimycobacterial activities (Mamolo, M. G. *et al*, 2004). A number of dihydropyridine (DHP) derivatives are employed as potential drug candidates for the treatment of congestive heart failure(Vo, D. *et al*, 1995). Moreover DHPs also act as NADH mimics for the reduction of carbonyl compounds and their derivatives (Rueping, M. *et al*, 2006). Bicyclic nitrogen-containing heterocyclic compounds, such as pyridopyrimidines is a well-known pharmacophore in drug discovery. Pyrido [2,3-d]pyrimidines have been the most thoroughly investigated of the four ring systems and hence, this scaffold is associated with a wide range of biological activities (Gautham S. K. *et al*, 2015; Brown, D. J. 1962; Makishima, I. *et al*, 1993; Agarwal, H. S. *et al*, 1998; Singh, G. *et al*, 2000; Bozing, D. *et al*, 1991; Nishikava, Y. *et al*, 1989; Hhigh, D. *et al*, 1996; Balakrishna Pai, S. *et al*, 1996; Verheggen, I. *et al*, 1993). Some analogues have been found to act as antitumor agents inhibiting dihydrofolate reductases or

tyrosine kinases (Gangjee, A., *et al*, 1999; Geffken, D. *et al*, 2011), while other are known antiviral agents(Nasr, M. N. *et al*, 2002). Chromenes are important oxygenated natural heterocyclic compounds of plant origin and serve as the basis of flavonoid structures (Yuan, L. *et al*, 2015; Zhao, W. *et al*, 2015; Santos, J.A.N. *et al*, 2016). Chromene derivatives endowed with wide range of biological activities such anticancer, anti-inflammatory, antibiotic, antitumor, antibacterial, antioxidant, antifungal, antimalarial, treatment of Alzheimer's disease and activity against the human immunodeficiency virus (HIV-1) etc (Jayashree, B.S. *et al*, 2016; Sun, Y.N. *et al*, 2016; Albrecht, U. *et al*., 2005; Göker, H. *et al*, 2005; Modranka, J. N. *et al*, 2006; Kim, S.H. *et al*, 2011; Ali, T. E.S. *et al*, 2007; Lerdsirisuk, P. *et al*, 2014; Liu, Q. *et al*, 2015; Ungwitayatorn, J. *et al*, 2004).

Pyranopyridines constitute an important class of heterocyclic compounds having diverse biological activities such as antiproliferative, cancer chemopreventive, anti-bacterial (including anti-tubercular), antimyopic, anti-histamic, hypotensive, anti-rheumatic, and antiasthmatic activities. (Tantivatana, P. *et al*, 1983; Yamada, N. *et al*, 1992; Kolokythas, G. *et al*, 2006; Azuine, M.A. *et al*, 2004; Srivastava, S.K. *et al*, 2005; Toshiro, S., Noriko, W. 1996; Ito, Y. *et al* 1994; Goto, K. *et al*, 1985; Maruyama, Y. *et al*, 1981; Ukawa, K. *et al*, 1985). Quinoline nucleus occurs in several natural compounds (Cinchona Alkaloids) and pharmacologically active substances displaying a broad range of biological activities such as antimalarial, antifungal, anthelmintic, cardiotonic, anticonvulsant, anti-inflammatory, antimycobacterial and analgesic activities(Kumar, S. *et al*, 2009; Singh, S. *et al*, 2015). Prompted by their recent synthetic protocol and diverse biological and pharmacological importance for drug discovery, we have been interested in developing efficient methodology for the synthesis of pyridine-fused medicinally privileged derivatives. Therefore, herein we have reported a simple, convenient, and efficient domino protocol for the effective synthesis of so far unexplored derivatives of 2,3-quinolinedicarboxylate, chromeno[4,3-b]pyridine-2,3-dicarboxylate, pyrido[2,3-d]pyrimidine-6,7-dicarboxylate, and pyrano[4,3-b]pyridine-2,3-dicarboxylate by one-pot, four-component coupling reaction utilizing 1,3 di carbonyl compound, aromatic aldehyde, aniline and dimethyl acetylenedicarboxylate as the versatile templates in the presence of Iron(III)chloride as catalyst in ethanol media.

RESULTS AND DISCUSSION

Initially, for optimization of the reaction conditions, we performed a multicomponent domino reaction of dimedone with benzaldehyde, aniline and dimethyl acetylenedicarboxy late to presumably afford 2,3-quinolinedicarboxylate under various conditions (Scheme 1). To optimise reaction conditions the model reaction was examined in different solvents such as methanol, ethanol, DMF and dichloromethane in the presence of various catalyst including $FeCl_3$, *p*-TSA and CuI under refluxing condition (Table 1). It was observed that ethanol in the presence of Iron (III)chloride is the solvent of choice for the reaction, as the desired product was obtained in excellent yield (Table 1, entry 6), while without catalyst trace product was formed after 4 hrs (Table 1, entry 7).



Scheme 1. Model reaction

Table 1. Optimization of the reaction condition on the synthesis of 5a

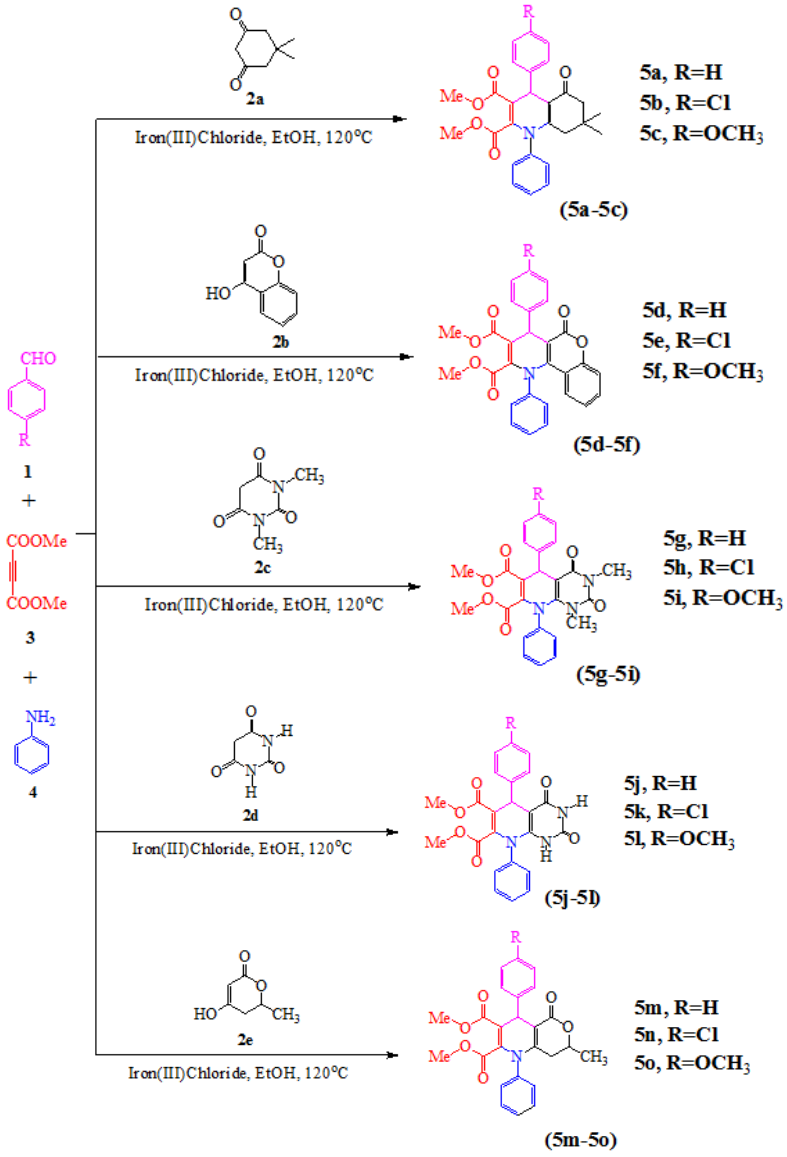
Entry	Solvent	Catalyst	time	yield (%)
1.	Methanol	$FeCl_3$	33 min	79
2.	Methanol	*p*-TSA	45 min	73
3.	Methanol	CuI	57 min	70
4.	Ethanol	*p*-TSA	32 min	81
5.	Ethanol	CuI	37 min	74
6.	Ethanol	$FeCl_3$	18 min	95
7.	Ethanol	No catalyst	more than 4 hrs	traces
8.	DMF	*p*-TSA	1 hrs 10 min	80
9.	DMF	CuI	54	78
10.	DMF	$FeCl_3$	46	84
11.	Dichloromethane	*p*-TSA	1 hrs 10 min	75
12.	Dichloromethane	CuI	1 hrs 17 min	72
13.	Dichloromethane	$FeCl_3$	58	80

Reaction conditions: benzaldehyde (1.0 mmol), dimethyl acetylenedicarboxylate (1.0 mmol), aniline(1.0 mmol), dimedone(1.0 mmol) and Iron(III)chloride(0.1 mmol).

In the course of our research work we have observed that Iron (III) chloride has a unique capability to enhance the reaction rate in ethanol. It was found that the best results were obtained with 10 mol % of Iron (III) chloride catalyst. The reaction was completed within 18 min and the product was obtained in 95% yield. We have also examined the effect of temperature on the reaction outcome in ethanol in the presence of Iron (III) chloride at different temperatures ranging from room temperature to refluxing (130 °C). The excellent yield of desired product 5a was obtained at 120 °C. Therefore, ethanol at 120 °C in the presence of 10 mol % of Iron (III)chloride was chosen as optimal conditions for all further reactions to afford structurally diverse pyridine fused heterocyclic derivatives (5a-5o) in excellent yields (87% - 95%) (Table 2). After optimization of the reaction conditions, to examine the scope of this protocol, particularly in regard to library construction, this methodology was evaluated by using substituted aromatic aldehydes 1, cyclic 1,3-dicarbonyl compounds 2a-2e, with dimethyl acetylenedicarboxylate 3 and aniline 4 for the library validation (Scheme 2). The selective formation of the very different pyridine fused heterocyclic derivatives depends on the structure of cyclic 1, 3-dicarbonyl compound.

MATERIALS AND METHODS

The melting points of all the synthesized compounds were determined on the electrothermal melting point apparatus using open capillary tube and are recorded uncorrected. All reagents and solvents were purchased from commercial sources and used without purification. The purity of all the synthesized compounds was checked by TLC. IR spectra were recorded on a Shimadzu 8400S FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 Advance Spectrometer at 300.13 and 75.47MHz, respectively.



(Scheme-2)

Table 2. Synthesis of Pyridine fused heterocycles(5a-5o)

Entry	R	Reaction time (min)	Yield (%)	M.p.(°C)
5a	H	18	95	213-214
5b	Cl	20	93	239-240
5c	OCH_3	25	88	258-259
5d	H	25	94	201-202
5e	Cl	28	91	192-193
5f	OCH_3	32	89	233-234
5g	H	27	90	235-236
5h	Cl	32	92	226-227
5i	OCH_3	37	87	229-230
5j	H	24	92	217-218
5k	Cl	29	93	220-221
5l	OCH_3	32	90	223-224
5m	H	22	94	237-238
5n	Cl	25	91	241-242
5o	OCH_3	29	92	263-264

In all cases, NMR spectra were obtained inDMSO-d6 using TMS as internal standard. The NMR signals are reported in δ ppm. Analytical and spectral data of the synthesized compounds are in agreement with their proposed structures.

Typical experimental procedure

A mixture of acetylenedicarboxylate(1.0 mmol), cyclic 1,3-diketone (1.0 mmol), aromatic aldehydes (1.0 mmol), aniline(1.0 mmol) and Iron(III)chloride(0.1 mmol) in Ethanol (5 mL) was stirred on a magnetic stirrer at 120°C for 18–40 min. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water and cooled ethanol to afford the product. The catalyst, Iron(III)chloride, being water soluble, was recovered from the filtrate.

Conclusion

In conclusion, we have devised a versatile, convenient, and efficient approach to synthesized structurally diverse pyridine fused heterosystem via four-component one-pot reaction using ethanol as a solvent, and Iron(III)chloride as an efficient and recyclable catalyst in quantitative yields. The operational simplicity, economic viability, atom-economy, together with ecologically benign nature make this protocol a very efficient alternative to literature methods, importantly of all, the purification procedure is just followed by filtration, washing and drying and the catalyst can be reused for the next cycle, so the waste can be reduced effectively.

5a) Dimethyl 7,7-di methyl-5-oxo-1,4-diphenyl-1,4,5,6,7,8-hexahydro-2,3-quinolinedicarboxylate, M.p. 213-214 °C, IR (KBr) ν(cm^{-1}): 1740, 1690, 1615, 1375, 1020, ^{1}H NMR (DMSO-d_6) δ(ppm): 1.11 (3H, s, CH_3), 1.12(3H, s, CH_3), 1.87 (2H, s, CH_2), 2.87 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.42(1H, s, CH), 6.45-7.16(10H, m, H-Ar),^{13}C NMR (DMSO-d_6) δ(ppm): 197.6, 165.1, 151.6, 146.7, 144.8, 137.8, 129.4, 129.1, 128.4, 125.6, 118.5, 115.3, 115.0, 108.3, 54.0, 50.4, 45.6, 28.5, 26.9,26.8, 17.5. Anal.Calcd(%) for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14; found C, 72.75; H, 6.08; N, 3.17.

5b)Dimethyl 4-(4-chlorophenyl)- 7,7-di methyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydro-2,3-quinolinedicarboxylate.
M.p. 239-240°C, IR (KBr) ν(cm^{-1}): 1752, 1675, 1605, 1360, 1025, ^{1}H NMR (DMSO-d_6) δ(ppm): 1.14 (3H, s, CH_3), 1.16(3H, s, CH_3), 1.85 (2H, s, CH_2), 2.84 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.40(1H, s, CH), 6.40-7.19(9H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 197.4, 165.2, 151.4, 146.5, 144.6, 135.8, 130.8, 129.4, 128.8, 118.4, 115.3, 115.1, 108.2, 54.0,, 50.8, 45.3, 28.7, 26.5, 26.5, 17.3. Anal.Calcd(%) for $C_{27}H_{26}ClNO_5$: C, 67.57; H, 5.46; N, 2.92; found C, 67.53; H, 5.42; N, 2.95.

5c) Dimethyl 4-(4-methoxyphenyl)- 7,7-di methyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydro-2,3-quinolinedicarboxylate.
M.p.258-259°C, IR (KBr) ν(cm^{-1}): 1740, 1685, 1620, 1375, 1045, 1022. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.11 (3H, s, CH_3), 1.12(3H, s, CH_3), 1.88 (2H, s, CH_2), 2.86 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 4.42(1H, s, CH), 6.45-7.01(9H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 197.6, 165.1, 165.0, 159.0, 151.6, 146.7, 144.8, 130.3, 129.3, 118.5, 115.0, 114.2, 108.6, 56.1, 54.0, 50.8, 45.6, 28.5, 26.8, 17.2. Anal.Calcd(%) for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95; found C, 70.69; H, 6.10; N, 2.99.

5d) Dimethyl 1,4-diphenyl-5-oxo -1,2-dihydro-5H-chromeno[4,3-b]pyridine-2,3-dicarboxylate. M.p.201-202 °C, IR (KBr) ν(cm^{-1}): 1733, 1669, 1605, 1365,1025, 1010. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.40(1H, s, CH), 6.40-7.62(14H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.0, 162.0,154.6, 150.8, 146.5, 144.5, 130.7, 129.4, 128.1, 127.7, 125.2, 121.3, 118.5,115.2, 96.3, 50.7, 29.6. Anal.Calcd (%) for $C_{28}H_{21}NO_6$: C, 71.94; H, 4.53; N, 3.00; found C, 71.90; H, 4.51; N, 3.04.

5e) Dimethyl -4-(4-chlorophenyl) -5-oxo- 1-phenyl -1,2-dihydro-5H-chromeno[4,3-b]pyridine-2,3-dicarboxylate.
.p.192-193°C, IR (KBr) ν(cm^{-1}): 1740, 1680, 1617, 1375, 1045, 1007. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.72 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.43(1H, s, CH), 6.46-7.63(13H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.1, 162.1, 154.0, 150.5, 146.7, 144.8, 137.8, 129.2, 128.4, 127.3, 126.6, 125.0, 121.1, 118.4, 115.3, 96.0, 50.8, 29.6. Anal.Calcd(%)for $C_{28}H_{20}ClNO_6$: C, 67.00; H, 4.02; N, 2.79; found C, 66.95; H, 3.94; N, 2.82.

5f) Dimethyl -4-(4-methoxyphenyl) -5-oxo- 1-phenyl- -1, 2-dihydro-5H-chromeno[4,3-b]pyridine-2,3-dicarboxylate.
M.p.233-234 °C, IR (KBr) ν(cm^{-1}): 1730, 1667, 1610, 1365, 1037, 1020. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.40(1H, s, CH), 6.42-7.63(13H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.0, 159.0, 154.2, 150.8, 146.4, 144.5, 130.2, 129.4, 128.1, 127.7, 126.9, 125.2, 121.3, 118.5, 115.1, 114.0, 96.3, 56.0, 50.4, 29.3. Anal.Calcd(%)for $C_{29}H_{23}NO_7$: C, 70.01; H, 4.66; N, 2.82; found C, 69.95; H, 4.60; N, 2.85.

5g) Dimethyl 1,3-Dimethyl-2,4-dioxo-5,8-diphenyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-d]pyrimidine-6,7-dicarboxylate.
M.p.235-236 °C, IR (KBr) ν(cm^{-1}): 1742, 1685, 1615, 1450, 1373, 1011. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.72 (3H, s, CH_3), 2.75 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.43(1H, s, CH), 6.46-7.14(10H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.1, 163.0, 153.5, 151.2, 146.7, 144.8, 137.7, 129.4, 128.4, 125.5, 118.4, 115.3, 79.7, 50.8, 30.6, 28.9, 28.3. Anal.Calcd(%)for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 5.02; N, 9.11; found C, 64.97; H, 5.00; N, 9.15.

5h) Dimethyl-5-(4-chlorophenyl)-1,3-Dimethyl-2,4-dioxo-8-phenyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-d]pyrimidine-6,7-dicarboxylate. M.p.226-227°C, IR (KBr) ν(cm^{-1}): 1733, 1665, 1625, 1435, 1364, 1025. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.71 (3H, s, CH_3), 2.73 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.41(1H, s, CH), 6.40-7.14(9H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.0, 163.3, 153.1, 146.3, 144.4, 135.8, 130.8, 129.3, 128.8, 118.5, 115.1, 79.4, 50.5, 30.6, 28.3. Anal.Calcd(%)for $C_{25}H_{22}ClN_3O_6$: C, 60.55; H, 4.47; N, 8.47; found C, 60.35; H, 4.40; N, 8.50.

5i)Dimethyl 5-(4-methoxyphenyl)-1,3-Dimethyl-2,4-dioxo-8-phenyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-d]pyrimidine-6,7-dicarboxylate. M.p.229-230 °C, IR (KBr) ν(cm^{-1}): 1742, 1685, 1615, 1450, 1375, 1045, 1018. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.72 (3H, s, CH_3), 2.74 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.43(1H, s, CH), 6.42-7.01(9H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.1, 163.0, 159.0, 153.5, 151.2, 146.7, 144.8, 130.2, 129.4, 118.5, 115.2, 114.1, 79.7, 56.0, 50.4, 30.6, 28.9. Anal.Calcd(%) for $C_{26}H_{25}N_3O_7$: C, 63.54; H, 5.13; N, 8.55; found C, 63.49; H, 5.09; N, 8.50.

5j) Dimethyl 2,4-dioxo-5,8-diphenyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-d]pyrimidine-6,7-dicarboxylate. M.p. 217-218 °C, IR (KBr) ν(cm^{-1}): 3356, 3173, 1700, 1650, 1615, 1020. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.71 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.41(1H, s, CH), 6.0(1H, s, NH), 6.46-7.15(10H, m, H-Ar), 10.0(1H, s, NH), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.0, 164.4, 151.5, 146.5, 144.3, 137.7, 129.3, 128.5, 125.5, 118.5, 115.3, 79.5, 50.8, 27.8. Anal.Calcd(%) for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.42; N, 9.70; found C, 63.70; H, 4.39; N, 9.75.

5k) Dimethyl 5-(4-chlorophenyl)-2,4-dioxo-8-phenyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-d]pyrimidine-6,7-dicarboxylate. M.p.220-221 °C, IR (KBr) ν(cm^{-1}): 3380, 3163,

1742, 1690, 1605, 1011. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.43(1H, s, CH), 6.1(1H, s, NH), 6.43-7.15(9H, m, H-Ar), 10.2(1H, s, NH), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.1, 164.2, 151.3, 146.7, 144.8, 135.7, 130.8, 129.4, 128.8, 118.3, 115.0, 79.7, 50.5, , 27.5. Anal.Calcd(%) for $C_{23}H_{18}ClN_3O_6$:C, 59.04; H, 3.88; N, 8.98; found C, 58.94; H, 3.80; N, 8.95.

5l) Dimethyl 5-(4-methoxyphenyl)-2,4-dioxo-8-phenyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-d]pyrimidine-6,7-dicarboxylate. M.p. 223-224 °C, IR (KBr) ν(cm^{-1}): 3366, 3145, 1730, 1671, 1614, 1044, 1021. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.72 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.41(1H, s, CH), 6.0(1H, s, NH), 6.40-7.17(9H, m, H-Ar), 10.1(1H, s, NH), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.3, 164.4, 159.0, 151.5, 146.4, 144.7, 130.3, 129.4, 118.5, 115.3, 114.1, 79.2, 56.1, 50.8, 27.7. Anal.Calcd(%) for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57; N, 9.07; found C, 62.10; H, 4.51; N, 9.17.

5m) Dimethyl 1,4-diphenyl-7-methyl-5-oxo-1,4,7,8-tetrahydro-5H-pyrano[4,3-b]pyridine-2,3-dicarboxylate. M.p.237-238 °C, IR (KBr) ν(cm^{-1}): 1741, 1665, 1611, 1374, 1039, 1012. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.98 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.43(1H, s, CH), 6.21(1H, s, CH), 6.46-7.14(10H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.1, 161.0, 155.7, 146.7, 144.8, 144.1, 137.7, 129.3, 128.3, 125.4, 118.4, 115.3, 102.7, 100.3, 50.4, 30.1, 22.4.Anal.Calcd(%) for $C_{25}H_{21}NO_6$: C, 69.60; H, 4.91; N, 3.25; found C, 69.51; H, 4.85; N, 3.20.

5n) Dimethyl 4-(4-chlorophenyl)-7-methyl-5-oxo-1-phenyl -1,4,7,8-tetrahydro-5H-pyrano[4,3-b]pyridine-2,3-dicarboxylate . M.p.241-242°C, IR (KBr) ν(cm^{-1}): 1733, 1644, 1604, 1364, 1039, 1007. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.94 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.40(1H, s, CH), 6.20(1H, s, CH), 6.42-7.19(9H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.0, 161.2, 155.4, 146.5, 144.4, 135.7, 130.6, 129.4, 128.8, 118.5, 115.0, 102.2, 50.8, 30.0, 22.1. Anal.Calcd(%)for $C_{25}H_{20}ClNO_6$: C, 64.45; H, 4.33; N, 3.01; found C, 64.38; H, 4.30; N, 3.05.

5o) Dimethyl 4-(4-chlorophenyl)-7-methyl-5-oxo-1-phenyl -1,4,7,8-tetrahydro-5H-pyrano[4,3-b]pyridine-2,3-dicarboxylate. M.p.263-264°C, IR (KBr) ν(cm^{-1}): 1740, 1670, 1612, 1371, 1089, 1039, 1017. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.98 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 4.43(1H, s, CH), 6.21(1H, s, CH), 6.46-7.01(9H, m, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 165.2, 161.0, 159.0, 155.7, 146.7, 144.8, 130.3, 129.5, 118.4, 115.3, 115.0, 114.1, 102.7, 100.3, 56.0, 50.8, 30.1, 22.5, Anal.Calcd(%) for $C_{26}H_{23}NO_7$:C, 67.67; H, 5.02; N, 3.04; found C, 67.61; H, 5.48; N, 3.10.

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