One-Pot Three-Component Synthesis of *Hantzsch* 1,4-Dihydropyridines Promoted by Dimethyl Phosphate Ionic Liquids

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A one-pot three-component reaction of ethyl acetoacetate, $AcONH_4$, and different aldehydes has been successfully performed in the presence of ionic liquids (ILs) possessing a $(MeO)_2PO_2^-$ counterion. The impact of electronic and steric effects of the substituents of aromatic aldehydes, as well as the influence of different anions of ILs on the product yield, have been investigated. The application of dimethyl phosphate ILs in the synthesis of *Hantzsch* 1,4-dihydropyridines presents a simple method for obtaining structurally diverse products in moderate to high yields without using any additional catalyst.

Introduction. – 1,4-Dihydropyridines (1,4-DHPs), originally described by *Hantzsch* [1], are important heterocyclic compounds with valuable pharmaceutical properties. Due to their antitumor, anti-inflammatory, anticonvulsant, and antitubercular activities, and high efficiency as Ca^{2+} channel blockers, 1,4-DHPs can be successfully exploited in tumor therapy and treatment of *Alzheimer*'s disease, cardiovascular disorders, hypertension, *etc.* [2]. Furthermore, a wide range of 1,4-DHPs may serve as useful synthetic intermediates [2a] as well as hydrogen equivalents for the reduction of α,β-unsaturated carbonyl compounds, cyclic/acyclic imines, and activated olefins [3].

The growing demand for structurally diverse 1,4-DHPs has led to manifold modifications of the procedure reported by *Hantzsch*. Different approaches concerning a particular selection of the solvent (H_2O [4], diethylene glycol [5], MeCN [6], MeOH [7], *etc.*), reagents (aldehyde, active methylene compound, source of nitrogen [2e][8]), catalyst (*Brønsted* acids and bases [9], *Lewis* acids and bases [10], organocatalysts [11], zeolites [12], *etc.*), and the reaction conditions (ultrasound or microwave irradiation, solvent-free protocols [13]) have been successfully applied in order to obtain 1,4-DHPs. However, exploitation of volatile and toxic molecular solvents and expensive catalysts, long reaction times, and tedious workup procedures may still be outlined as some important drawbacks that should be overcome to provide more efficient and environmentally benigner synthetic methods.

Some of these limitations have been eliminated by using ionic liquids (ILs) – structurally diverse compounds with beneficial properties (negligible vapor pressure, thermal and chemical stability, catalytic activity, *etc.*) [14]. Hence, several protocols for synthesizing 1,4-DHPs in the presence of ILs have been developed [15]. *Zolfigol* and co-workers have demonstrated an extensive application of *Brønsted* acidic ILs (1,3-disulfo-1*H*-imidazol-3-ium hydrogen sulfate ([Dsim][HSO_4]), [pyridine–SO_3H][Cl], and 1-methyl-1*H*-imidazol-3-ium trinitromethanide ([HC_1im][$C(NO_2)_3$])) as efficient catalysts for the preparation of polyhydroquinolines [16]. Furthermore,

Yadav et al. have exploited 1-butyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate ($[C_4C_1im][PF_6]$) and $[C_4C_1im][BF_4]$ as solvents for a one-pot three-component *Hantzsch* reaction [17]. *Perumal et al.* and *Shi et al.* have reported the synthesis of 1,4-DHP derivatives in $[C_4C_1im][Cl]$ and $[C_4C_1im][Br]$, respectively [18].

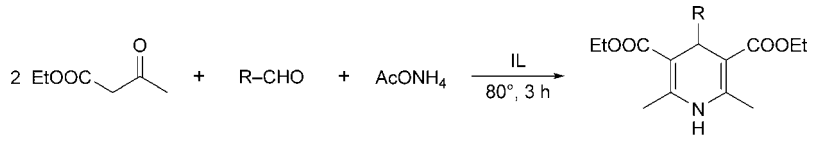
These previously developed methods encouraged us to continue our initial studies concerning ILs with a $(MeO)_2PO_2^-$ counterion [19]. Several examples of applying these salts in condensation reactions [20] implied the possibility to use them also for obtaining 1,4-DHPs. Consequently, we report here a new, advantageous approach – the one-pot three-component reaction of ethyl acetoacetate, $AcONH_4$, and different aldehydes performed in the presence of dimethyl phosphate ILs.

Results and Discussion. – In order to clarify the suitability of dimethyl phosphate ILs for the synthesis of 1,4-DHPs, a model reaction, according to the *Scheme*, between ethyl acetoacetate (**1**), 4-methoxybenzaldehyde (**2l**), and $AcONH_4$ in the presence of $[C_4C_1im][(MeO)_2PO_2]$ (**4**) was studied first. We proposed that this new approach would allow performing the reaction without any additional catalyst and thereby serve as an alternative synthetic method. In addition, the hydrophilic IL **4** could be easily removed by dissolution in H_2O to obtain the crude product.

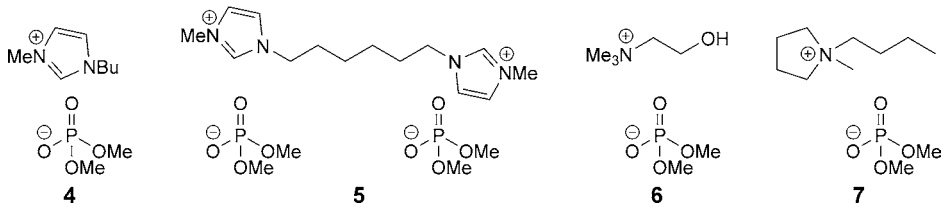
Completion of the model reaction, as indicated by TLC, was achieved in 3 h, and the highest yield (60%; *Table 1*, *Entry 12*) of product **3l** was obtained using 1.0 equiv. of aldehyde **2l**, 2.0 equiv. of ethyl acetoacetate (**1**), 1.5 equiv. of $AcONH_4$, and 2.0 equiv. of IL **4**. Amounts of IL **4** differing from 2.0 equiv. (0.5, 1.0, and 4.0 equiv.) provided decreased yields of 1,4-DHP **3l** (41, 49, and 49%, resp.). Since ILs **4**–**7** (*Fig.*), possessing structurally divergent cations (singly or doubly charged, aromatic or aliphatic) and a $(MeO)_2PO_2^-$ counterion, provided similar yields of product **3l**, IL **4** was selected as a representative for further investigation of the method.

From a synthetic point of view, the desirable approach, requiring no additional catalyst and keeping the workup procedure to be simple, challenged us to utilize the

Scheme. *Synthesis of 1,4-Dihydropyridines from Ethyl Acetoacetate, $AcONH_4$, and Different Aldehydes*



1 **2a – 2m** **3a – 3m**



4 **5** **6** **7**

Figure. *Structures of ionic liquids* **4**–**7**

Table 1. *Synthesis of 1,4-DHPs* **3a**–**3m** *in the Presence of* $[C_4C_1im][(MeO)_2PO_2]$ (**4**)[a])

Entry	Aldehyde	R	Product	Yield [%][b])
1	**2a**[c])	H	**3a**	83
2	**2b**	Ph	**3b**	61
3	**2c**	4-Cl–C_6H_4	**3c**	80
4	**2d**	3-Cl–C_6H_4	**3d**	66
5	**2e**	4-Br–C_6H_4	**3e**	73
6	**2f**	3-Br–C_6H_4	**3f**	73
7	**2g**	2-Br–C_6H_4	**3g**	71
8	**2h**	4-F–C_6H_4	**3h**	62
9	**2i**	2-F–C_6H_4	**3i**	64
10	**2j**	3-O_2N–C_6H_4	**3j**	64
11	**2k**	4-HO–C_6H_4	**3k**	51
12	**2l**	4-MeO–C_6H_4	**3l**	60
13	**2m**	PhCH=CH	**3m**	50

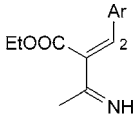
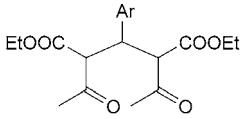
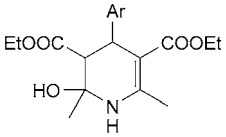
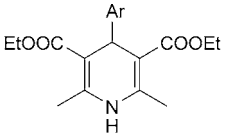
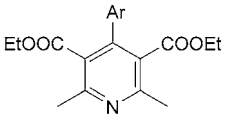
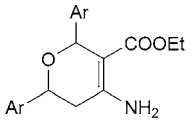
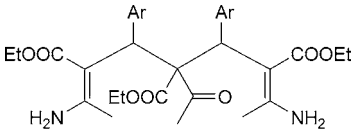
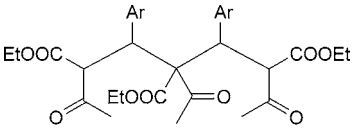
[a]) A mixture of 2.0 equiv. of ethyl acetoacetate (**1**; 6.30 mmol), 1.0 equiv. of aldehyde **2** (3.15 mmol), 1.5 equiv. of $AcONH_4$ (4.73 mmol), and 2.0 equiv. of IL (6.30 mmol) was stirred at 80° for 3 h. [b]) Yield of isolated product. [c]) 1.0 Equiv. of hexamethylenetetramine (3.15 mmol) was used as source of HCHO (**2a**).

selected conditions for obtaining some other 1,4-DHPs. *Table 1* demonstrates the scope of aldehydes for this method. Reaction of ethyl acetoacetate (**1**), $AcONH_4$, and aldehydes **2a**–**2m** provided the respective 1,4-DHPs **3a**–**3m** in moderate to high yields. Product **3a** (83%; *Table 1*, *Entry 1*) was obtained using an excess of HCHO (**2a**) formed *in situ* from hexamethylenetetramine (1.0 equiv.). The application of a stoichiometric amount (1.0 equiv.) of HCHO (**2a**), provided by 0.2 equiv. of hexamethylenetetramine, resulted in a noticeably decreased yield of **3a** (54%). As a result, the structural diversity of aromatic aldehydes that may be exploited for this approach has been emphasized.

As reported in the literature, electronic and steric effects of the substituents of aromatic aldehydes may significantly affect the yields of desired products [21]. Therefore, we expected the yields of 1,4-DHPs **3c**–**3l** (*Table 1*, *Entries 3–12*) to increase with the growing reactivity of substituted benzaldehydes X–C_6H_4–CHO, where $X = OH < MeO < F < Cl < Br < NO_2$. In order to evaluate the impact of the substituent, all reactions were performed strictly under the same conditions (*Scheme*). The results obtained (*Table 1*) were mostly consistent with the aforementioned sequence of the reactivity for aromatic aldehydes. Surprisingly, no steric effect on the yield of products **3e**–**3i** (*Table 1*, *Entries 5–9*) was observed by varying the position of F and Br in the respective benzaldehydes. Substrates with no substitution (*Table 1*, *Entry 2*) or bearing electron-donating substituents (*Table 1*, *Entries 11* and *12*) tended to provide lower yields of the target 1,4-DHPs than aldehydes with electron-withdrawing groups (*Table 1*, *Entries 3–9*). However, the yield of **3j** (*Table 1*, *Entry 10*) was not as high as expected. Moreover, when 4-nitrobenzaldehyde was used instead of 3-nitrobenzaldehyde (**2j**), a complex mixture of the product **3n**, intermediates **8**–**10**, and different side products was obtained, as indicated by HPLC. The plausible structures of the detected compounds, including some of the side products, **11**–**14**, were

confirmed by HR-ESI-MS (*Table 2*). Previously reported insights into the mechanism of the *Hantzsch* 1,4-DHP synthesis clarify that the NO_2 group, possessing an exceptionally high ability of electron-withdrawal, may be responsible for the lack of stabilization of the positive charge at C(2) of intermediate **8** in the transition state [21c]. Based on this, we propose that the application of 3-nitrobenzaldehyde (**2j**) and 4-nitrobenzaldehyde in the synthesis of 1,4-DHPs, promoted by dimethyl phosphate ILs, may be restricted due to some favorable nucleophilic attacks at C(2) in **8** thus leading to an undesired *Michael* addition reaction (side products **13** and **14**, *Table 2*) and reduced yields of the target products. Moreover, the increased consumption of ethyl acetoacetate (**1**) could possibly lead to another structurally different compound, **12**. The potential formation and the structure of this side product were proposed according to

Table 2. *Plausible Structures of Compounds Formed in the Synthesis of 1,4-DHP* **3n**[a])

Entry	Structure[b])	*Entry*	Structure[b])
1	 **8** *m/z* 263.1020 ([*M* + H]$^+$; calc. 263.1026)	*2*	 **9** *m/z* 394.1491 ([*M* + H]$^+$; calc. 394.1496)
3	 **10** *m/z* 393.1651 ([*M* + H]$^+$; calc. 393.1656)	*4*	 **3n** *m/z* 375.1560 ([*M* + H]$^+$; calc. 375.1551)
5	 **11** *m/z* 373.1399 ([*M* + H]$^+$; calc. 373.1394)	*6*	 **12** *m/z* 414.1286 ([*M* + H]$^+$; calc. 414.1296)
7	 **13** *m/z* 655.2610 ([*M* + H]$^+$; calc. 655.2610)	*8*	 **14** *m/z* 657.2288 ([*M* + H]$^+$; calc. 657.2290)

[a]) A mixture of 2.0 equiv. of ethyl acetoacetate (**1**; 6.30 mmol), 1.0 equiv. of 4-nitrobenzaldehyde (3.15 mmol), 1.5 equiv. of $AcONH_4$ (4.73 mmol), and 2.0 equiv. of IL **4** (6.30 mmol) was stirred at 80° for 3 h. The mixture was analyzed with HPLC, and the structures of **8**–**10**, **3n**, and **11**–**14** were confirmed by HR-ESI-MS. [b]) Ar = 4-O_2N–C_6H_4.

the investigation reported earlier [22]. *Michael* addition involving the C=C bond of *trans*-cinnamaldehyde (**2m**) may be also responsible for the moderate yield of 1,4-DHP **3m**.

In order to clarify the possible beneficial role of $(MeO)_2PO_2^-$, the effect of different IL anions on this three-component reaction was evaluated and 4-chlorobenzaldehyde (**2c**) was selected as a representative substrate. Compared to solvent-free conditions and application of other salts that possess the $[C_4C_1im]^+$ cation, IL **4** allowed synthesizing product **3c** in the highest yield (80%; *Table 3*, *Entry 1*). These results confirmed that dimethyl phosphate IL **4** can be successfully exploited in the synthesis of *Hantzsch* 1,4-DHPs, thus providing a promising synthetic method.

Table 3. *Synthesis of 1,4-DHP* **3c** *in the Presence of Ionic Liquids with 1-Butyl-3-methyl-1*H*-imidazol-3-ium Cation and Different Anions*

Entry	IL	Yield of **3c** [%][a])
1	$[C_4C_1im][(MeO)_2PO_2]$ (**4**)	80
2	$[C_4C_1im][Cl]$	73
3	$[C_4C_1im][Br]$	74
4	$[C_4C_1im][PF_6]$	61[b])
5	$[C_4C_1im][NTf_2]$	31[c])
6	$[C_4C_1im][OMs]$	68
7	$[C_4C_1im][OTs]$	70
8	None	37

[a]) Yield of isolated product. [b]) The mixture, after cooling to r.t., was extracted with ^{t}BuOMe (7×6 ml). The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. [c]) 1 ml of ice-cold EtOH was added to the mixture. The resulting precipitate was kept at $-20°$ for 2 h and then filtered. The crude products were recrystallized from EtOH/H_2O 3 : 1.

Conclusions. – In conclusion, a convenient synthesis of structurally diverse 1,4-DHPs promoted by ILs possessing a $(MeO)_2PO_2^-$ counterion has been demonstrated for the very first time. The possibility to perform this one-pot three-component reaction without any additional catalyst, simple workup procedure, and broad aldehyde scope make this method a practically useful and cost-efficient synthetic tool.

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Experimental Part

General. All chemicals were purchased from *Sigma–Aldrich* and were used without any further purification. M.p.: *Stuart SMP3* apparatus; uncorrected. HPLC: *Agilent 1290 Infinity* LC system; *Waters Xterra C18* column (3.5 μm, 150×2.1 mm). FT-IR Spectra: *PerkinElmer FT-IR/FIR Frontier* instrument; ATR film; ν in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Varian 400 MR* spectrometer (400.0 and 100.6 MHz, resp.); in (D_6)DMSO; δ in ppm rel. to residual solvent peak as internal reference, J in Hz. HR-ESI-MS: *Agilent 6230 TOF LC/MS* mass spectrometer; in m/z.

Synthesis of ILs **4**–**7** *and [C_4C_1im][Cl], [C_4C_1im][Br], [C_4C_1im][PF_6^-], [C_4C_1im][NTf_2^-], [C_4C_1im][OMs], and [C_4C_1im][OTs].* ILs were obtained according to the procedures reported previously: 1-butyl-3-methyl-1*H*-imidazol-3-ium dimethyl phosphate ([C_4C_1im][$(MeO)_2PO_2$]; **4**), 1,1′-hexane-1,6-diylbis(3-methyl-1*H*-imidazol-3-ium) bis(dimethyl phosphate) (**5**), (2-hydroxyethyl)trimethylammonium dimethyl phosphate (**6**), 1-butyl-1-methylpyrrolidinium dimethyl phosphate (**7**) [19], 1-butyl-3-methyl-1*H*-imidazol-3-ium chloride ([C_4C_1im][Cl]) [23], 1-butyl-3-methyl-1*H*-imidazol-3-ium bromide ([C_4C_1im][Br]) [24], 1-butyl-3-methyl-1*H*-imidazol-3-ium Hexafluorophosphate [C_4C_1im][PF_6] [25], 1-butyl-3-methyl-1*H*-imidazol-3-ium bis[(trifluoromethyl)sulfonyl]azanide ([C_4C_1im][NTf_2]) [25], 1-butyl-3-methyl-1*H*-imidazol-3-ium methanesulfonate ([C_4C_1im][OMs]) [26], and 1-butyl-3-methyl-1*H*-imidazol-3-ium *p*-toluenesulfonate ([C_4C_1im][OTs]) [27].

General Procedure for the Synthesis of Hantzsch *1,4-DHPs in the Presence of IL.* A mixture of 2.0 equiv. of ethyl acetoacetate (**1**; 6.30 mmol, 0.82 g), 1.0 equiv. of aldehyde **2** (3.15 mmol), 1.5 equiv. of $AcONH_4$ (4.73 mmol, 0.36 g), and 2.0 equiv. of IL (6.30 mmol) was stirred at 80° for 3 h. After cooling to r.t., 15 ml of dist. H_2O were added, and the obtained semi-solid was mixed for several minutes until a precipitate was formed. The resulting crude product was filtered, washed on the filter with additional 15 ml of dist. H_2O, and recrystallized from EtOH or EtOH/H_2O 3 : 1. The pure product was dried *in vacuo* (0.6 mbar, 45°, 2 h).

Workup Procedure for the Synthesis of Hantzsch *1,4-DHPs in the Presence of Hydrophobic ILs.* When using [C_4C_1im][PF_6], the mixture, after cooling to r.t., was extracted with ^{t}BuOMe (7 × 6 ml). The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. In the case of [C_4C_1im][NTf_2], 1 ml of ice-cold EtOH was added to the mixture. The resulting precipitate was kept at −20° for 2 h and then filtered. All crude products were purified and dried according to the general procedure.

The analytical data for 1,4-DHPs, synthesized in the presence of [C_4C_1im][$(MeO)_2PO_2$] (**4**), are given below.

Diethyl 1,4-Dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3a**). 1.0 Equiv. of hexamethylenetetramine (3.15 mmol, 0.44 g) was used as source of HCHO (**2a**). Yield: 0.66 g (83%). Yellow solid. M.p. 173–175° (176° [28]). FT-IR: 3348, 2988, 1691, 1648. ^{1}H-NMR: 8.26 (*s*, 1 H); 4.05 (*q*, *J* = 7.1, 4 H); 3.11 (*s*, 2 H); 2.11 (*s*, 6 H); 1.18 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 167.1; 146.5; 97.0; 58.9; 24.7; 17.9; 14.4. HR-ESI-MS: 254.1387 ([*M* + H]$^+$, $C_{13}H_{20}NO_4^+$; calc. 254.1387).

Diethyl 1,4-Dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (**3b**). Yield: 0.63 g (61%). Yellow solid. M.p. 156–158° (156–158° [10c]). FT-IR: 3340, 2984, 1686, 1649. ^{1}H-NMR: 8.79 (*s*, 1 H); 7.24–7.04 (*m*, 5 H); 4.86 (*s*, 1 H); 4.06–3.90 (*m*, 4 H); 2.25 (*s*, 6 H); 1.12 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.9; 148.1; 145.3; 127.8; 127.3; 125.9; 101.8; 59.0; 18.2; 14.2. HR-ESI-MS: 330.1701 ([*M* + H]$^+$, $C_{19}H_{24}NO_4^+$; calc. 330.1700).

Diethyl 4-(4-Chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3c**). Yield: 0.92 g (80%). Yellow solid. M.p. 145–147° (145–147° [10c]). FT-IR: 3357, 2986, 1694, 1650. ^{1}H-NMR: 8.84 (*s*, 1 H); 7.20 (*dd*, *J* = 43.1, 8.4, 4 H); 4.84 (*s*, 1 H); 4.05–3.91 (*m*, 4 H); 2.25 (*s*, 6 H); 1.12 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.8; 147.1; 145.6; 130.4; 129.2; 127.8; 101.5; 59.1; 38.5; 18.2; 14.2. HR-ESI-MS: 364.1308 ([*M* + H]$^+$, $C_{19}H_{23}ClNO_4^+$; calc. 364.1310).

Diethyl 4-(3-Chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3d**). Yield: 0.76 g (66%). Yellow solid. M.p. 136–138° (140–142° [10c]). FT-IR: 3320, 2980, 1701, 1648. ^{1}H-NMR: 8.88 (*s*, 1 H); 7.25 (*t*, *J* = 7.7, 1 H); 7.20–7.08 (*m*, 3 H); 4.84 (*s*, 1 H); 4.07–3.91 (*m*, 4 H); 2.26 (*s*, 6 H); 1.13 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.7; 150.5; 145.9; 132.3; 129.9; 127.2; 126.1; 125.9; 101.3; 59.1; 18.3; 18.2; 14.1. HR-ESI-MS: 364.1312 ([*M* + H]$^+$, $C_{19}H_{23}ClNO_4^+$; calc. 364.1310).

Diethyl 4-(4-Bromophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3e**). Yield: 0.94 g (73%). Yellow solid. M.p. 160–162° (160–162° [29]). FT-IR: 3359, 2984, 1692, 1650. ^{1}H-NMR: 8.84 (*s*, 1 H); 7.24 (*dd*, *J* = 120.6, 8.4, 4 H); 4.82 (*s*, 1 H); 4.05–3.90 (*m*, 4 H); 2.25 (*s*, 6 H); 1.13 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.7; 147.5; 145.6; 130.7; 129.6; 118.9; 101.4; 59.1; 18.2; 14.2. HR-ESI-MS: 430.0617 ([*M* + Na]$^+$, $C_{19}H_{22}BrNNaO_4^+$; calc. 430.0624).

Diethyl 4-(3-Bromophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3f**). Yield: 0.94 g (73%). Yellow solid. M.p. 113–115° (115–117° [30]). FT-IR: 3322, 2980, 1670, 1648. ^{1}H-NMR: 8.88 (*s*, 1 H); 7.32–7.26 (*m*, 2 H); 7.21–7.11 (*m*, 2 H); 4.83 (*s*, 1 H); 4.07–3.93 (*m*, 4 H); 2.26 (*s*, 6 H); 1.13 (*t*, *J* =

7.1, 6 H). ^{13}C-NMR: 166.7; 150.8; 145.9; 130.2; 128.7; 126.4; 121.0; 109.6; 101.3; 59.1; 18.2; 14.1. HR-ESI-MS: 408.0798 ($[M+H]^+$, $C_{19}H_{23}BrNO_4^+$; calc. 408.0805).

Diethyl 4-(2-Bromophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3g**). Yield: 0.91 g (71%). Yellow solid. M.p. 131–134° (140–141° [31]). FT-IR: 3324, 2978, 1696, 1670. ^{1}H-NMR: 8.81 (*s*, 1 H); 7.41 (*d*, *J* = 8.0, 1 H); 7.32 (*dd*, *J* = 7.8, 1.7, 1 H); 7.25 (*t*, *J* = 7.4, 1 H); 7.01 (*td*, *J* = 7.9, 1.7, 1 H); 5.20 (*s*, 1 H); 4.04–3.91 (*m*, 4 H); 2.22 (*s*, 6 H); 1.10 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.9; 148.1; 145.1; 132.3; 131.3; 127.8; 121.6; 102.1; 58.9; 18.2; 18.1; 14.3. HR-ESI-MS: 408.0804 ($[M+H]^+$, $C_{19}H_{23}BrNO_4^+$; calc. 408.0805).

Diethyl 4-(4-Fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3h**). Yield: 0.68 g (62%). Slightly yellow solid. M.p. 147–149° (147–149° [32]). FT-IR: 3341, 2985, 1686, 1650. ^{1}H-NMR: 8.82 (*s*, 1 H); 7.20–7.11 (*m*, 2 H); 7.01 (*t*, *J* = 8.9, 2 H); 4.85 (*s*, 1 H); 4.06–3.91 (*m*, 4 H); 2.26 (*s*, 6 H); 1.12 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.8; 160.6; 145.4; 144.4; 129.1; 114.4; 101.8; 59.0; 38.3; 18.2; 14.2. HR-ESI-MS: 348.1595 ($[M+H]^+$, $C_{19}H_{23}FNO_4^+$; calc. 348.1606).

Diethyl 4-(2-Fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3i**). Yield: 0.70 g (64%). Yellow solid. M.p. 156–159° (148–152° [33]). FT-IR: 3330, 2982, 1692, 1650. ^{1}H-NMR: 8.80 (*s*, 1 H); 7.22 (*td*, *J* = 7.6, 1.7, 1 H); 7.17–7.08 (*m*, 1 H); 7.07–6.92 (*m*, 2 H); 5.11 (*s*, 1 H); 4.00–3.85 (*m*, 4 H); 2.24 (*s*, 6 H); 1.08 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.7; 159.9; 157.4; 145.7; 135.6; 130.7; 127.8; 124.0; 114.7; 101.1; 58.9; 33.2; 18.1; 13.9. HR-ESI-MS: 348.1602 ($[M+H]^+$, $C_{19}H_{23}FNO_4^+$; calc. 348.1606).

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (**3j**). Yield: 0.75 g (64%). Yellow solid. M.p. 156–158° (158–160° [30]). FT-IR: 3344, 2990, 1704, 1644, 1523, 1346. ^{1}H-NMR: 8.99 (*s*, 1 H); 8.03–7.94 (*m*, 2 H); 7.61 (*d*, *J* = 7.7, 1 H); 7.53 (*d*, *J* = 7.7, 1 H); 4.97 (*s*, 1 H); 4.06–3.89 (*m*, 4 H); 2.28 (*s*, 6 H); 1.12 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.5; 150.3; 147.4; 146.4; 134.2; 129.6; 121.9; 121.1; 101.1; 59.2; 18.2; 14.1. HR-ESI-MS: 375.1551 ($[M+H]^+$, $C_{19}H_{23}N_2O_6^+$; calc. 375.1551).

Diethyl 1,4-Dihydro-4-(4-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**3k**). Yield: 0.56 g (51%). Yellow solid. M.p. 226–228° (225–229° [34]). FT-IR: 3345, 2988, 1655. ^{1}H-NMR: 9.05 (*s*, 1 H); 8.69 (*s*, 1 H); 6.75 (*dd*, *J* = 140.9, 8.5, 4 H); 4.74 (*s*, 1 H); 4.05–3.90 (*m*, 4 H); 2.23 (*s*, 6 H); 1.13 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 167.1; 155.4; 144.7; 138.9; 128.3; 114.5; 102.3; 58.9; 37.9; 18.2; 14.2. HR-ESI-MS: 346.1652 ($[M+H]^+$, $C_{19}H_{24}NO_5^+$; calc. 346.1649).

Diethyl 1,4-Dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**3l**). Yield: 0.68 g (60%). Yellow solid. M.p. 155–157° (156° [35]). FT-IR: 3340, 2984, 1687, 1648. ^{1}H-NMR: 8.74 (*s*, 1 H); 6.90 (*dd*, *J* = 117.3, 8.7, 4 H); 4.79 (*s*, 1 H); 4.05–3.91 (*m*, 4 H); 3.67 (*s*, 3 H); 2.24 (*s*, 6 H); 1.13 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 167.0; 157.4; 145.0; 140.5; 128.3; 113.2; 102.1; 58.9; 54.9; 37.9; 18.2; 14.2. HR-ESI-MS: 360.1818 ($[M+H]^+$, $C_{20}H_{26}NO_5^+$; calc. 360.1805).

*Diethyl 1,4-Dihydro-2,6-dimethyl-4-[(*E*)-2-phenylethenyl]pyridine-3,5-dicarboxylate* (**3m**). Yield: 0.56 g (50%). Yellow solid. M.p. 141–142° (141–143° [21d]). FT-IR: 3334, 2979, 1687, 1639. ^{1}H-NMR: 8.81 (*s*, 1 H); 7.32–7.13 (*m*, 5 H); 6.14–5.99 (*m*, 2 H); 4.46 (*d*, *J* = 5.3, 1 H); 4.16–3.99 (*m*, 4 H); 2.25 (*s*, 6 H); 1.19 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 166.8; 146.3; 137.1; 132.2; 128.5; 127.1; 126.9; 126.0; 99.2; 59.0; 36.0; 18.2; 14.4. HR-ESI-MS: 356.1853 ($[M+H]^+$, $C_{21}H_{26}NO_4^+$; calc. 356.1856).

REFERENCES

[1] A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.

[2] a) R. Lavilla, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 1141; b) G. Swarnalatha, G. Prasanthi, N. Sirisha, C. M. Chetty, *Int. J. ChemTech Res.* **2011**, *3*, 75; c) D. J. Triggle, *Mini-Rev. Med. Chem.* **2003**, *3*, 215; d) N. Edraki, A. R. Mehdipour, M. Khoshneviszadeh, R. Miri, *Drug Discovery Today* **2009**, *14*, 1058; e) A. Saini, S. Kumar, J. S. Sandhu, *J. Sci. Ind. Res.* **2008**, *67*, 95.

[3] T. Marcelli, in 'Enantioselective Organocatalyzed Reactions I: Enantioselective Oxidation, Reduction, Functionalization and Desymmetrization', Ed. R. Mahrwald, Springer Netherlands, Dordrecht, 2011, p. 43; S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407; J. Che, Y. Lam, *Adv. Synth. Catal.* **2010**, *352*, 1752; A. N. Ivchenko, A. N. Balaev, E. A. Ruchko, V. E. Fedorov, *Chem. Heterocycl. Compd. (N.Y., NY, U.S.)* **2014**, *50*, 285.

[4] J. Yang, C. Jiang, J. Yang, C. Qian, D. Fang, *Green Chem. Lett. Rev.* **2013**, *6*, 262; G.-W. Wang, J.-J. Xia, C.-B. Miao, X.-L. Wu, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 454.
[5] N. Tewari, N. Dwivedi, R. P. Tripathi, *Tetrahedron Lett.* **2004**, *45*, 9011.
[6] B. Das, M. Srilatha, B. Veeranjaneyulu, B. S. Kanth, *Helv. Chim. Acta* **2011**, *94*, 885.
[7] G. Prasanthi, K. V. S. R. G. Prasad, K. Bharathi, *Eur. J. Med. Chem.* **2014**, *73*, 97.
[8] J.-P. Wan, Y. Liu, *RSC Adv.* **2012**, *2*, 9763.
[9] S. R. Cherkupally, R. Mekala, *Chem. Pharm. Bull.* **2008**, *56*, 1002; G. C. Nandi, S. Samai, M. S. Singh, *J. Org. Chem.* **2010**, *75*, 7785; W. H. Correa, J. L. Scott, *Green Chem.* **2001**, *3*, 296; L. Shen, S. Cao, J. Wu, H. Li, J. Zhang, M. Wu, X. Qian, *Tetrahedron Lett.* **2010**, *51*, 4866.
[10] a) L.-M. Wang, J. Sheng, L. Zhang, J.-W. Han, Z.-Y. Fan, H. Tian, C.-T. Qian, *Tetrahedron* **2005**, *61*, 1539; b) S. Kikuchi, M. Iwai, H. Murayama, S.-I. Fukuzawa, *Tetrahedron Lett.* **2008**, *49*, 114; c) A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati, B. Carboni, *Tetrahedron Lett.* **2009**, *50*, 5248.
[11] C.-L. Shi, H. Chen, D. Shi, *J. Heterocycl. Chem.* **2012**, *49*, 125; S. M. Baghbanian, S. Khaksar, S. M. Vahdat, M. Farhang, M. Tajbakhsh, *Chin. Chem. Lett.* **2010**, *21*, 563.
[12] B. Das, B. Ravikanth, R. Ramu, B. Vittal Rao, *Chem. Pharm. Bull.* **2006**, *54*, 1044; S. S. Katkar, P. H. Mohite, L. S. Gadekar, B. R. Arbad, M. K. Lande, *Green Chem. Lett. Rev.* **2010**, *3*, 287.
[13] P. Kaur, H. Sharma, R. Rana, D. N. Prasad, R. K. Singh, *Asian J. Chem.* **2012**, *24*, 5649.
[14] J. P. Hallett, T. Welton, *Chem. Rev. (Washington, DC, U.S.)* **2011**, *111*, 3508; N. V. Plechkova, K. R. Seddon, *Chem. Soc. Rev.* **2008**, *37*, 123; H. Olivier-Bourbigou, L. Magna, D. Morvan, *Appl. Catal., A* **2010**, *373*, 1; K. Ghandi, *Green Sust. Chem.* **2014**, *4*, 44; R. F. M. Frade, C. A. M. Afonso, *Hum. Exp. Toxicol.* **2010**, *29*, 1038.
[15] N. Isambert, M. del Mar Sanchez Duque, J.-C. Plaquevent, Y. Génisson, J. Rodriguez, T. Constantieux, *Chem. Soc. Rev.* **2011**, *40*, 1347; M. Li, W.-S. Guo, L.-R. Wen, Y.-F. Li, H.-Z. Yang, *J. Mol. Catal. A: Chem.* **2006**, *258*, 133; K. Pajuste, A. Plotniece, K. Kore, L. Intenberga, B. Cekavicus, D. Kaldre, G. Duburs, A. Sobolev, *Cent. Eur. J. Chem.* **2011**, *9*, 143; B. P. Reddy, K. Rajesh, V. Vijayakumar, *Arab. J. Chem.* **2015**, *8*, 138; A. Rajendran, C. Karthikeyan, K. Rajathi, *Int. J. ChemTech Res.* **2011**, *3*, 810.
[16] A. Zare, F. Abi, A. R. Moosavi-Zare, M. H. Beyzavi, M. A. Zolfigol, *J. Mol. Liq.* **2013**, *178*, 113; A. Khazaei, M. A. Zolfigol, A. R. Moosavi-Zare, J. Afsar, A. Zare, V. Khakyzadeh, M. H. Beyzavi, *Chin. J. Catal.* **2013**, *34*, 1936; M. A. Zolfigol, S. Baghery, A. R. Moosavi-Zare, S. M. Vahdat, H. Alinezhad, M. Norouzi, *RSC Adv.* **2014**, *4*, 57662.
[17] J. S. Yadav, B. V. S. Reddy, A. K. Basak, A. V. Narsaiah, *Green Chem.* **2003**, *5*, 60.
[18] R. Sridhar, P. T. Perumal, *Tetrahedron* **2005**, *61*, 2465; D.-Q. Shi, S.-N. Ni, F. Yang, J.-W. Shi, G.-L. Dou, X.-Y. Li, X.-S. Wang, *J. Heterocycl. Chem.* **2008**, *45*, 653.
[19] E. Priede, E. Bakis, A. Zicmanis, *Synlett* **2014**, *25*, 2447.
[20] B. Alici, S. Köytepe, T. Seçkin, *Turk. J. Chem.* **2007**, *31*, 569; S. Zhang, L. D. Goncalves, H. Lefebvre, M. Tessier, B. Rousseau, A. Fradet, *ACS Macro Lett.* **2012**, *1*, 1079; N. Wehofsky, C. Wespe, V. Cerovsky, A. Pech, E. Hoess, R. Rudolph, F. Bordusa, *ChemBioChem* **2008**, *9*, 1493.
[21] a) L. E. Hinkel, W. R. Madel, *J. Chem. Soc.* **1929**, 750; b) L. E. Hinkel, E. E. Ayling, W. H. Morgan, *J. Chem. Soc.* **1931**, 1835; c) J. V. Urošević, S. Ž. Drmanić, J. B. Nikolić, I. O. Juranić, B. Ž. Jovanović, *J. Serb. Chem. Soc.* **2013**, *78*, 1963; d) S.-X. Wang, Z.-Y. Li, J.-C. Zhang, J.-T. Li, *Ultrason. Sonochem.* **2008**, *15*, 677; e) L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96; f) O. Exner, S. Böhm, *Curr. Org. Chem.* **2006**, *10*, 763.
[22] M. Filipan-Litvić, M. Litvić, I. Cepanec, V. Vinković, *Molecules* **2007**, *12*, 2546.
[23] L. Crowhurst, P. R. Mawdsley, J. M. Perez-Arlandis, P. A. Salter, T. Welton, *Phys. Chem. Chem. Phys.* **2003**, *5*, 2790.
[24] C. C. Weber, A. F. Masters, T. Maschmeyer, *Org. Biomol. Chem.* **2013**, *11*, 2534.
[25] A. G. Porras-Gutiérrez, J. Zeitouny, A. Gomila, B. Douziech, N. Cosquer, F. Conan, O. Reinaud, P. Hapiot, Y. Le Mest, C. Lagrost, N. Le Poul, *Dalton Trans.* **2014**, *43*, 6436.
[26] S. Ivanova, L. F. Bobadilla, A. Penkova, F. R. Sarria, M. A. Centeno, J. A. Odriozola, *Catalysts* **2011**, *1*, 52.
[27] P. D. Vu, A. J. Boydston, C. W. Bielawski, *Green Chem.* **2007**, *9*, 1158.

[28] D. R. Patil, D. S. Dalal, *Lett. Org. Chem.* **2011**, *8*, 477.
[29] A. Heydari, S. Khaksar, M. Tajbakhsh, H. R. Bijanzadeh, *J. Fluorine Chem.* **2009**, *130*, 609.
[30] C.-C. Chang, S. Cao, S. Kang, L. Kai, X. Tian, P. Pandey, S. F. Dunne, C.-H. Luan, D. J. Surmeier, R. B. Silverman, *Bioorg. Med. Chem.* **2010**, *18*, 3147.
[31] M. A. Zolfigol, P. Salehi, M. Safaiee, *Lett. Org. Chem.* **2006**, *3*, 153.
[32] W. Pei, Q. Wang, X. Li, L. Sun, *Chin. J. Chem.* **2010**, *28*, 483.
[33] K. L. Bridgwood, G. E. Veitch, S. V. Ley, *Org. Lett.* **2008**, *10*, 3627.
[34] B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi, E. Macko, *J. Med. Chem.* **1974**, *17*, 956.
[35] B. Datta, M. A. Pasha, *Chin. J. Catal.* **2011**, *32*, 1180.

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