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ORIGINAL PAPER

Synthesis of Hantzsch poly-substituted pyridines containing adamantyl moiety

Mina Abkar Aras[1] · **Adeleh Moshtaghi Zonouz**[1]

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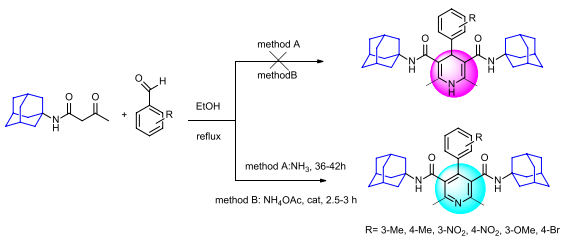
Abstract

A one-step procedure has been developed for the synthesis of new Hantzsch poly-substituted pyridines from a three-component reaction of *N*-(adamantan-1-yl)acetoacetamide, aldehyde derivatives, ammonium acetate in ethanol in the presence of montmorillonite K10 catalyst under reflux conditions. The presence of adamantyl moiety in adamantyl acetoacetamide as an active methylene component leads to a strong steric hindrance and accelerates the oxidation of 1,4-dihydropyridines to the pyridine derivatives. The use of montmorillonite catalyst leads to a simple procedure of synthesis and short reaction times. As a result, facile workup, simple reaction procedure, good yields, and economical process are advantages of this one-pot multicomponent reaction.

Graphical abstract



Keywords Poly-substituted pyridine · Adamantane moiety · Hantzsch reaction · Multi-component reaction · Montmorillonite K10

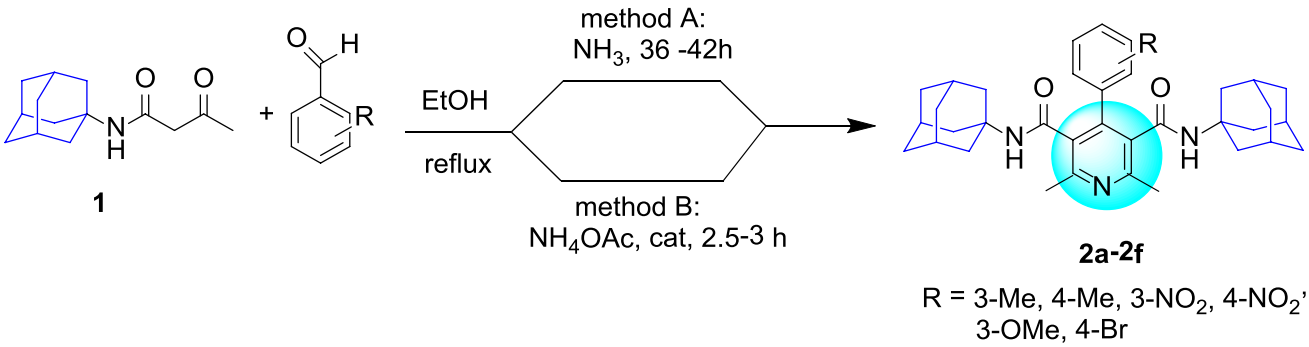
Introduction

Multicomponent reactions (MCRs) are known as particular forms of chemically useful organic reactions, in which three or more different compounds react to form a final product in a one-pot process. These approaches are eco-friendly, highly atom-economical, and synthetically effective in terms of stages, energy, reduced time, material consumption, and solvents [1]. The 1,4-dihydropyridine heterocyclic ring is a common feature of various bioactive compounds such as antihypertensive [2], anticancer [3, 4], antitumor [5], anricipable [6], anti-inflammatory [7], and antidiabetic agents [8]. The most common method for the synthesis of this compounds is the Hantzsch synthesis, which involves condensation of an aldehyde, β-ketoester, and ammonia in ethanol as solvent [9]. Dihydropyridines in turn may also be converted to substituted pyridines through oxidation by oxidants such as DDQ [10], MnO_2 [11], $Mn(OAc)_3/NaIO_4$ [12], air [13]. Pyridines because of their prevalence in natural products and drugs attract considerable interest in organic synthesis and medicinal chemistry. In addition, poly- substituted pyridines have attracted increasing attention due to various pharmacological applications such as antimitotic agents [14], anti-inflammatory agents [15], and anticonvulsants. 2-Amino-3-cyanopyridine derivatives have raised significant response as potent inhibitors of HIV-1 [16].

✉ Mina Abkar Aras
m86.abkar@gmail.com

[1] Department of Chemistry, Faculty of Science, Azarbaijan Shahid Madani University, Tabriz, Iran

Scheme 1



Besides, adamantane, with 10 C and 16 H, is a tricyclic cage molecule with high symmetry and many applications especially in medicinal chemistry. Adamantane-based drug such as amantadine for the treatment of influenza A [17, 18] and an anti-Parkinson [19], rimantadine [20] and tromantadine [21] for the treatment an antiviral agents, adapalene for the treatment of acne patients and anti-inflammatory [22], dopamantine to treat Parkinson's disease [23], vildagliptin [24], and saxagliptin [25] for the treatment of type 2 diabetes was approved and exist in market.

The unique properties of adamantane, such as lipophilicity, rigid cage, dimensions and bulkiness, have caused scientists to use it to design new compounds with novel biological properties or to modify parent drugs and biologically active compounds. Therefore numerous compounds containing adamantyl moiety were proved to possess a broad spectrum of biological activities such as antiviral [26, 27], anti-Parkinson [28, 29], anticancer [30], antibacterial [31], treatment of COVID-19 [32, 33], and treatment for neurological disease [34].

In the literature, only a few examples of pyridine containing adamantyl have been synthesized. For example in 1974 Ludwig Bauer and co-workers reported the synthesis of 2,3-(1-adamantanethio)pyridines, 1-acetyl-2-(1-adamantanethio)-3-hydroxy-4-acetoxy-1,2,3,4-tetrahydropyridine, and the 3-acetoxy derivatives [35]. In 2001 Zygmunt Kazimierczuk and co-workers reported synthesis a series of (1-adamantyl)aminopyridine derivatives. The adamantyl compounds, particularly 2-(1-adamantyl)amino-6-methylpyridine, were found to be potent TNF-α inducers in murine melanoma cells transduced with gene for human TNF-α [36]. In 2016, Xin Han and co-workers synthesized a series of adamantane substituted imidazo-pyridine derivatives through a one-pot multi-component Groebke-Blackburn-Bienaymé reaction [37]. However, there is no report on the synthesis of poly-substituted pyridines containing adamantyl moiety. In recent years, heterogeneous catalysts have received considerable attention in chemical synthesis [38, 39]. Their use is favored because of their particularly versatile properties, low cost and thermal stability [40]. In addition, reactions catalyzed by solid supports or in a solid state provide better selectivity in the products, compared to solution phase reactions. These heterogeneous catalysts have found widespread application in eco-sustainable organic synthesis, showing higher activity than homogeneous catalysts [41]. In this regard, montmorillonite represents an ideal heterogeneous eco-sustainable catalyst thanks to its low cost, ease of handling, easy recovery by filtration method [42]. It is widely available and has a high surface area containing both Brønsted and Lewis acid sites catalyzing organic reactions [43].

In view of the diverse pharmacological properties of adamantane and poly-substituted pyridine derivatives, and following our previous studies on the synthesis of compounds containing adamantane derivatives [44], we report herein the synthesis and characterization of novel poly-substituted pyridine derivatives containing adamantane moiety in the classical route of Hantzsch reaction (absence of catalyst) and in the presence of montmorillonite as an efficient heterogeneous catalyst.

Results and discussion

As mentioned above, 1,4-dihydropyridines are generally synthesized using the Hantzsch method, which includes the condensation of aldehyde derivatives, *β*-ketoester, and ammonia in ethanol as solvent. Therefore, we used this method for the synthesis of 1,4-dihydropyridines containing adamantyl moiety.

According to the Scheme 1, the reaction of 2 equivalents of a *N*-(adamantan-1-yl)acetoacetamide (**1**) [41] as active methylene compound, 1 equivalent of 4-methylbenzaldehyde, and ammonia solution (25%) in ethanol under reflux conditions was obtained a white precipitated solid after about 38 h. Interestingly, the usual spectroscopic results showed that the product was 2,6-dimethyl-4-(4-methylphenyl) pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)-amide instead of our expected substituted 1,4-dihydropyridine derivative i.e. 3,5-di(1-adamantylcarbamoyl)-2,6-dimethyl-

4-(4-methylphenyl)-1,4-dihydropyridine. The IR spectrum of 2,6-dimethyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide confirmed the presence of the functional groups NH at 3290 cm^{-1} and the amide carbonyl (NH–C=O) as a strong absorption band in 1632 cm^{-1}. The ^{1}H NMR spectrum showed adamantane protons at 1.34 (t, 12H, Ad), 1.46 (s, 12H, Ad), 1.72 (s, 6H, Ad) ppm, and the two NH protons at 5.78 ppm. The ^{13}C NMR spectrum further confirmed the product by the presence of an amide carbonyl signal at 166.4 ppm. The presence of C=C signals at 137.4, 153.5 ppm was another reason for confirming the formation of this product.

In the ^{1}H NMR spectrum, the disappearance of two signals in the 4–5 ppm region, which are related to the N–H and CH-4 of the 1,4-dihydropyridine ring, and also in the ^{13}C NMR spectrum, the disappearance of a peak related to the C-4 in the aliphatic region and the presence of a peak (C=C) in the aromatic region showed that instead of totally substituted 1,4- dihydropyridine ring poly-substituted pyridine skeleton was formed. Also, the results of mass analysis confirmed the synthesis of 2,6-dimethyl-4-(4-methylphenyl)-pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide compound.

The reaction conditions were then applied to a range of aldehyde substrates. The results with different aldehydes are depicted in Table 1. Therefore, we assumed that the long reaction time caused the oxidation of 1,4-dihydropyridine to pyridine during the reflux by air with no additives. In the second method, the reaction of 2 equivalents of *N*-(adamantan-1-yl)acetoacetamide, 1 equivalent of 4-methylbenzaldehyde and ammonium acetate in the presence of the montmorillonite also produced the same product **2b** in 2.5 h (Scheme 1).

The products **2a**–**2f** were also produced through the reaction of *N*-(adamantan-1-yl)acetoacetamide, aldehyde derivatives, and ammonium acetate in the presence of the montmorillonite in 2.5–3 h. In these methods spatially hindered aldehydes (2-methoxy, 2-methyl, and 2-hydroxy substituted) did not give the desired products (Table 1). The synthesis of pyridine ring instead of 1,4-dihydropridine in two methods may be due to presence two adamantyl moiety in one scaffold that creates strong steric hindrance and accelerates oxidation. In both the two method pure products were obtained in good yields, without using any chromatographic techniques, simply by filtration and recrystallization.

Conclusion

In this study, we have successfully synthesized a series of novel 2,6-dimethyl-4-arylpyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide derivatives through a multi-component Hantzsch reaction of aromatic aldehyde, *N*-(adamantan-1-yl)acetoacetamide (**1**), ammonium acetate in the presence of montmorillonite K10 as an efficient heterogeneous catalyst. The presence of adamantyl moiety in adamantyl acetoacetamide as an active methylene component leads to a strong steric hindrance and accelerates the oxidation of 1,4-dihydropyridines to the pyridine derivatives. The results with different aldehyde components demonstrated the ortho substituted aryl aldehydes lead to a reduction in reactivity and lack of product formation due to steric hindrance. The use of a montmorillonite catalyst reduced the reaction time from 40 to 3 h. Thus, facile workup, simple reaction procedure, good yields, and economical process are advantages of one-pot multicomponent reactions.

Table 1 Synthesis of pyridine containing adamantyl moiety **2**, method A[a] and B[b]

Entry	R	Product	Time/h method A	Yield/%[c]	Time/h method B	Yield/%[c]
1	3-Me	**2a**	38	76	2.5	70
2	4-Me	**2b**	38	84	2.5	80
3	3-NO_2	**2c**	40	86	3	82
4	4-NO_2	**2d**	42	76	3	74
5	3-OMe	**2e**	36	72	2.5	72
6	4-Br	**2f**	40	77	3	72
7	2-Me	**2g**	40	–	3	–
8	2-OMe	**2h**	40	Trace	3	–
9	2-OH	**2i**	40	–	3	–

[a]Reaction conditions: benzaldehyde derivatives (1 mmol), *N*-(adamantan-1-yl)acetoacetamide (**1**, 2 mmol), ammonia solution 25% (1 mmol), 10 cm^3 solvent at reflux

[b]Reaction conditions: benzaldehyde derivatives (1 mmol), *N*-(adamantan-1-yl)acetoacetamide (**1**, 2 mmol), ammonium acetate (1.5 mmol), and montmorillonite as catalyst, 10 cm^3 solvent at reflux

[c]Yield of isolated pure product after recrystallization

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on Varian INOVA-500 NMR spectrometer. The IR spectra were recorded on a Bruker PS-15 spectrometer. The melting points were measured on an Electrothermal 9100 apparatus in open capillaries. The elemental analyses were performed on a Carlo-Erba 1104 CHN analyzer**.** The MASS spectra were recorded on an Agilent Technologies 5975C System. All the commercial reagents were used without prior purification.

Typical procedures for the synthesis of pyridine derivatives 2a-2i

Method A: To a mixture of *N*-(adamant-1-yl)acetoacetamide (**1**, 470 mg, 2 mmol), 3-methoxybenzaldehyde (0.121 cm^3, 1 mmol), in ethanol (10 cm^3) was added ammonia solution (25%, 18 mm^3, 1 mmol). The mixture was stirred at reflux temperature until completion of the reaction as indicated by TLC (40 h). Ammonia solution was added every 8 h during the reflux. The white precipitated solid was filtered, washed with water, and recrystallized from EtOH.

Method B: To a mixture of *N*-(adamant-1-yl)acetoacetamide (**1**, 470 mg, 2 mmol), 3-methoxybenzaldehyde (0.121 cm^3, 1 mmol), ammonium acetate (0.11 g, 1.5 mmol), in ethanol (10 cm^3) was added montmorillonite K10 (0.1 g). The mixture was stirred at reflux temperature until completion of the reaction as indicated by TLC (2.5 h). After the reaction completed, the solid catalyst was filtered and washed with ethanol. After activating the catalyst at 100 °C, it was used for the further reaction. The solvent was removed with a rotary evaporator. The residue washed with water and recrystallized from EtOH.

2,6-Dimethyl-4-(3-methylphenyl)pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide (2a, $C_{36}H_{45}N_3O_2$) Yield: method A 210 mg (76%), method B 190 mg (70%); white solid; m.p.: > 250 °C; IR (KBr): $\bar{\upsilon}$ = 3285 (NH), 2907, 2850 (C–H), 1631 (NH–C=O), 1552 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.57, 1.63 (d, J = 12 Hz, 12H, Ad), 1.76 (s, 12H, Ad), 1.96 (s, 6H, Ad), 2.36 (s, 3H, Ar–CH_3), 2.57 (s, 3H, CH_3-2,-6), 7.05–7.08 (m, 1H, Ar–H), 7.09 (s, 1H, Ar–H), 7.17 (d, J = 4.5 Hz, 1H, Ar–H), 7.28 (s, 1H, Ar–H), 7.67 (s, 2H, 2 NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 21.7 (Ar–CH_3), 21.8 (CH_3-2,-6), 28.6 (C–Ad), 35.9 (C–Ad), 40.4 (C–Ad), 51.1 (C–Ad), 126.8, 127.5, 127.9, 129.2, 129.8, 130.9 (C–Ar), 152.0 (=C), 166.1 (C=O) ppm.

2,6-Dimethyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide (2b, $C_{36}H_{45}N_3O_2$) Yield: method A 230 mg (84%), method B 220 mg (80%); colorless crystal; m.p.: > 250 °C; IR (KBr): $\bar{\upsilon}$ = 3290 (NH), 2910, 2852 (C–H), 1632 (NH–C=O), 1553 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.34 (t, J = 15 Hz, 12H, Ad), 1.46 (s, 12H, Ad), 1.72 (s, 6H, Ad), 2.15 (s, 3H, Ar–CH_3), 2.34 (s, 6H, CH_3-2,-6), 5.78 (s, 2H, 2 NH), 6.96 (d, J = 8 Hz, 2H, Ar–H), 7.04 (d, J = 8 Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 20.8 (Ar–CH_3), 21.9 (CH_3-2,-6), 28.8 (6C–Ad), 35.8 (6C–Ad), 40.5 (6C–Ad), 51.7 (2C–Ad), 128.1 (C_3, C_5), 128.4 (C_2, C_6), 130.6 (C_4), 132.6 (C_1), 137.4 (=C), 153.5 (=C), 166.4 (C=O) ppm; HRMS (ESI): *m/z* calcd for $C_{36}H_{45}N_3O_2$ (M^+) 551.3511, found 551.5.

2,6-Dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide (2c, $C_{35}H_{42}N_4O_4$) Yield: method A 250 mg (86%), method B 240 mg (82%); white solid; m.p.: > 250 °C; IR (KBr): $\bar{\upsilon}$ = 3390, 3248 (NH), 2907, 2851 (C–H), 1640 (NH–C=O), 1571 (C=C), 1534, 1349 (NO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.47, 1.53 (d, J = 12 Hz, 12H, Ad), 1.64 (s, 12H, Ad), 1.87 (s, 6H, Ad), 2.45 (s, 6H, CH_3-2,-6), 7.68 (t, J = 8 Hz, 1H, Ar–H), 7.8 (d, J = 7.5 Hz, 1H, Ar–H), 7.88 (s, 2H, 2 NH), 8.25 (d, J = 8 Hz, 1H, Ar–H), 8.30 (s, 1H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 21.7 (CH_3-2,-6), 28.6 (6C–Ad), 35.9 (6C–Ad), 40.4 (6C–Ad), 51.2 (2C–Ad), 122.5 (C_5), 124.2 (C_6), 128.8 (C_4), 130.6 (C_2), 135.9 (C_1), 137.6 (C_3), 140.9 (=C_1), 146.7 (=C), 152.4 (=C), 165.7 (C=O) ppm.

2,6-Dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide (2d, $C_{35}H_{42}N_4O_4$) Yield: method A 220 mg (76%), method B 215 mg (74%); white solid; m.p.: > 250 °C; IR (KBr): $\bar{\upsilon}$ = 3294 (NH), 2909, 2852 (C–H), 1631 (NH–C=O), 1554 (C=C), 1525, 1355 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.56 (d, J = 12 Hz, 12H, Ad), 1.66 (s, 12H, Ad), 1.96 (s, 6H, Ad), 2.60 (s, 6H, CH_3-2,-6), 5.14 (s, 2H, 2 NH), 7.55 (d, J = 8.5 Hz, 2H, Ar–H), 8.27 (d, J = 8.5 Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 22.5 (CH_3-2,-6), 29.3 (6C–Ad), 36.2 (6C–Ad), 40.3 (6C–Ad), 52.9 (2C–Ad), 123.3 (C_2, C_6), 130.4 (C_3, C_5) ppm.

2,6-Dimethyl-4-(3-methoxyphenyl)pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide (2e, $C_{36}H_{45}N_3O_3$) Yield: method A 200 mg (70%), method B 205 mg (72%); white solid; m.p.: > 250 °C; IR (KBr): $\bar{\upsilon}$ = 3359, 3245 (NH), 2906, 2850 (C–H), 1640 (NH–C=O), 1570 (C=C), 1308 (C–N), 1039 (C–O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.57, 1.62 (d, J = 12 Hz, 12H, Ad), 1.75 (s, 12H, Ad), 1.97 (s, 6H, Ad), 2.57 (s, 6H, CH_3-2,-6), 3.80 (s, 3H, Ar–OCH_3), 6.94 (d, J = 8.5 Hz, 1H, Ar–H), 7.00 (d, J = 7 Hz, 1H, Ar–H), 7.05 (s, 1H, Ar–H), 7.27 (t, J = 8.5 Hz, 1H, Ar–H), 7.63 (s, 2H, 2 NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 21.7

(CH_3-2,-6), 28.6 (6C–Ad), 36.0 (6C–Ad), 40.4 (6C–Ad), 51.0 (2C–Ad), 54.9 (Ar–OCH_3), 113.2 (C_4), 115.0 (C_2), 121.5 (C_6), 127.8 (C_5), 130.8 (C_1), 137.1 (C_3), 143.2 (=C), 152.0 (=C), 157.9 (=C), 166.1 (C=O) ppm.

2,6-Dimethyl-4-(4-bromophenyl)pyridine-3,5-dicarboxylic acid bis(adamantan-1-yl)amide (2f, $C_{35}H_{42}BrN_3O_2$) Yield: method A 230 mg (77%), method B 215 mg (72%); white solid; m.p.: > 250 °C; IR (KBr): $\bar{\upsilon}$ = 3288 (NH), 2907, 2850 (C–H), 1633 (NH–C=O), 1552 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.41 (s, 12H, Ad), 1.53 (s, 12H, Ad), 1.80 (s, 6H, Ad), 2.40 (s, 6H, CH_3-2,-6), 6.01 (s, 2H, 2 NH), 7.14 (d, J = 8 Hz, 2H, Ar–H), 7.34 (d, J = 8.5 Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.9 (C–Ad), 36.0 (C–Ad), 40.6 (C–Ad), 51.7 (C–Ad), 130.6 (C–Ar) ppm.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00706-023-03164-2.

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Data availability The data that support the findings of this study are available from the corresponding author.

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