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An efficient three-component domino synthesis of difluoromethyl-containing 1,4-dihydropyridines under solvent and catalyst free conditions

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The difluoromethyl-containing Hantzsch 1,4-dihydropyridines were synthesized in good yields by a one-pot cyclocondensation of ethyl difluoroacetoacetate (EDFAA), a variety of aromatic aldehydes and ammonium acetate under solvent and catalyst free conditions. The comparison of reaction conditions and products was made among the different 1,3-carbonyl substrates (ethyl acetoacetate, ethyl difluoroacetoacetate and ethyl trifluoroacetoacetate) for the Hantzsch reaction.

three-component, difluoromethyl, 1,4-dihydropyridines, ethyl difluoroacetoacetate

1 Introduction

Recently, difluoromethyl-containing compounds have been increasingly applied in pharmaceuticals, agrochemicals and other fields as the incorporation of the difluoromethyl group into biologically active compounds often gives rise to unique physiological activities [1–6]. Therefore, much effort has been made to develop novel and efficient methods to introduce the difluoromethyl group into molecules [7, 8]. The ethyl difluoroacetoacetate is a commercially available difluorinated building block, which can undergo several reactions to form difluoromethyl-containing compounds [8–10]. However, little is known about the reactivity, properties and products of this useful difluoro-containing building block when it is used as a component in the multicomponent reactions which is a powerful tool for the construction of diverse and complex molecules. There are only a few scattered reports concerning three-component reactions based on ethyl difluoroacetoacetate [11]. Herein, we report a novel and efficient synthesis of the difluoromethyl-containing 1,4-dihydropyridines under solvent and catalyst free conditions without additional dehydrating agent (Scheme 1).

2 Results and discussion

At the initiation of the modified Hantzsch reaction, the condensation of ethyl difluoroacetoacetate (EDFAA) with benzaldehyde and ammonium acetate has been selected as a model reaction to investigate the reaction conditions (Scheme 2). Generally, the catalyst plays a key role in determining the speed of the conventional Hantzsch reaction [12, 13]. However, our preliminary experiments showed that the reaction could proceed efficiently in the absence of the catalyst and the reaction time was not significantly shortened in the presence of catalysts such as piperidine. The next step in our study was to focus on the search for the optimum reaction conditions.

Recently, much of our effort has involved the development

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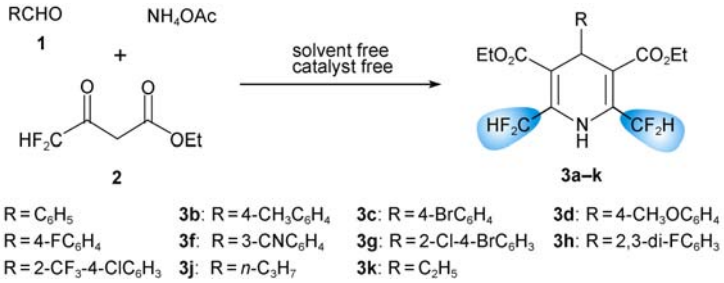
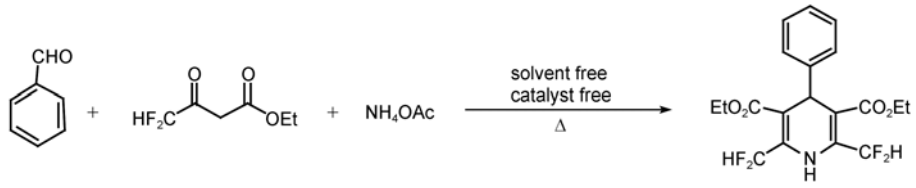


Scheme 1 Synthesis of difluoromethyl containing 1,4-dihydropyridines **3a–k** under solvent and catalyst free conditions.



Scheme 2 Model reaction for the synthesis of **3a** under solvent and catalyst free conditions.

of the multicomponent reactions such as Hantzsch reaction under solvent-free conditions [14–17]. Thus, the first experiments were conducted at different temperatures under solvent-free conditions. Table 1 shows the yields of products were strongly dependent on the temperature. The higher yield was obtained at 100 °C, whereas a further increase in temperature showed no improvement in the yield. Although the desired product was also obtained in boiling ethanol, long reaction time has been required and the yield was unsatisfactory.

In addition, effects of the molar ratio of benzaldehyde to EDFAA to ammonium acetate on this reaction were also investigated. It was found that when the molar ratio was 1:2.4:1, the reaction was finished within 5 h to give satisfactory yield (83%) at 100 °C under solvent-free condition. An increase in the amount of EDFAA or ammonium acetate could not enhance the yield of the product.

Under the optimized reaction condition, a variety of aldehydes were used to react with EDFAA and ammonium acetate to synthesize the desired 1,4-dihydropyridines. Both aliphatic and aromatic aldehydes could give good yields of 1,4-dihydropyridines. Furthermore, the presence of electron-withdrawing or electron-donating substituents on the aromatic ring did not make any difference in the yield of the product.

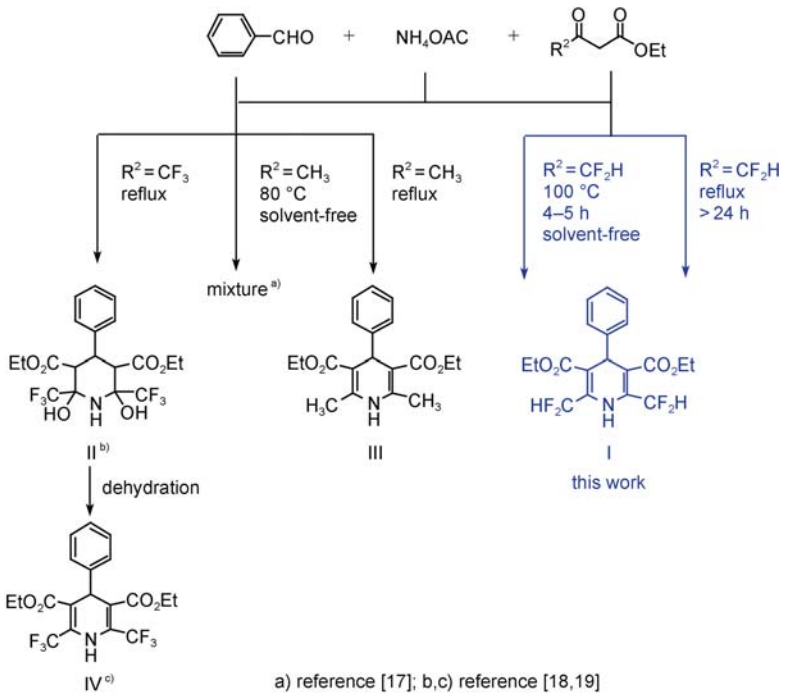
Table 1 Yields for the synthesis of **3a** under the solvent-free condition at different temperatures

Temperature (°C)	Solvent	Time (h)	Yield (%) [a,b]
reflux	ethanol	>24	72
rt	neat	>48	15
40	neat	>48	30
60	neat	>48	47
80	neat	12	68
100	neat	5	80
120	neat	5	81

a) Yields were based on GC analysis; b) the molar ratio of benzaldehyde to EDFAA to ammonium acetate is 1:2:1.

For comparison, the reaction conditions and products of different types of 1,3-dicarbonyl substrates (ethyl acetoacetate, ethyl difluoroacetoacetate and ethyl trifluoroacetoacetate) for the Hantzsch reaction are summarized in Scheme 3. When ethyl acetoacetate served as the substrate, cyclization reaction took place with low selectivity and low yield at 80 °C under solvent-free condition and gave mixtures of 1,4- and 1,2-dihydropyridine [17]. The classical 1,4-dihydropyridine (III) was the major product when the reaction was conducted in the presence of the catalysts under standard Hantzsch conditions. In the case of ethyl trifluoroacetoacetate, the corresponding 2,6-bis(trifluoromethyl)-2,6-dihydroxy-4-phenyl-3,5-pip-eridinedicarboxylate (II) was obtained in refluxing ethanol for several hours. This intermediate could be further dehydrated to 1,4-dihydropyridine (IV) by using suitable dehydration agents such as sulfuric acid, toluenesulfonic acid and trifluoroacetic anhydride [18, 19]. As to our work in this paper, no matter what the reaction conditions were, under reflux conditions or solvent free conditions, the reaction of ethyl difluoroacetoacetate with aldehyde and ammonium acetate yielded the 1,4-DHP product in good yield in the absence of catalysts. The undesired products such as undehydrated products and the isomers of 1,4-dihydropyridine were not observed. Scheme 3 shows the number of fluorine atoms on methyl group in ethyl acetoacetate has a significant impact on the process of Hantzsch reaction and the formation of products.

In conclusion, we report an efficient and practical approach to the synthesis of difluoromethyl-containing 1,4-dihydropyridines through a solvent and catalyst free one-pot



Scheme 3 The comparison of reaction conditions and products among the different 1,3-carbonyl substrates for the Hantzsch reaction.

three-component condensation of ethyl difluoroacetoacetate, aldehydes and ammonium acetate without additional dehydrating agent.

3 Experimental

3.1 Materials and instruments

All reagents were of analytic grade and obtained from commercial suppliers and used without further purification. Melting points were measured in an open capillary using Büchi melting point B-540 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as the internal standard. The ^{19}F NMR was obtained using a Bruker AM-400 spectrometer (376 MHz) and measured with external CF_3CO_2H as the standard. $CDCl_3$ was used as NMR solvent for all cases. Gas chromatography-mass spectra (GC-MS) were recorded on HP 5973 MSD with 6890 GC. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer. Column chromatography was carried out with Merck 60 (230–400 mesh) silica gel.

3.2 General procedure for the synthesis of 3a–k

To a stirred ethyl difluoroacetoacetate (2.4 mmol), aldehyde (1 mmol) and ammonium acetate (1.2 mmol) were added. The mixture was stirred at 100 °C for 4–5 h until the reaction was completed (monitored by TLC). Then, the reaction mixture was treated with brine solution (10 mL), extracted with dichloromethane (3 × 10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to leave the crude product which was purified by chromatography over silica gel.

*Diethyl 2,6-bis(difluoromethyl)-4-phenyl-1,4-dihydro pyridine-3,5-dicarboxylate (**3a**)*

Yield 75% (isolated yield and the same below), white solid, mp 88.1–88.3 °C. ^{1}H NMR: δ = 1.26 (t, J = 7.2 Hz, 6H), 4.13–4.21 (m, 4H), 5.10 (s, 1H), 7.07 (s, 1H), 7.21–7.29 (m, 5H), 7.44 (t, J_{HF} = 54.4 Hz, 2H) ppm; ^{13}C NMR: δ = 14.0, 39.7, 61.2, 108.4 (t, $^3J_{CF}$ = 5.6 Hz), 108.9 (t, $^1J_{CF}$ = 239.4 Hz), 127.4, 128.1, 128.5, 137.4 (t, $^2J_{CF}$ = 22.1 Hz), 144.8, 165.0 ppm; ^{19}F NMR: δ = −121.5 (d, J = 54.4 Hz, 2F), −121.8 (d, J = 54.4 Hz, 2F) ppm; HRMS (EI) for $C_{19}H_{19}F_4NO_4$, calcd: 401.1250, found: 401.1251.

*Diethyl 2,6-bis(difluoromethyl)-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3b**)*

Yield 77%, white solid, mp 92.1–92.4 °C. ^{1}H NMR: δ = 1.27 (t, J = 7.1 Hz, 6H), 2.31 (s, 3H), 4.13–4.20 (m, 4H), 5.05 (s, 1H), 7.03 (s, 1H), 7.08–7.18 (m, 4H), 7.42 (t, J_{HF} = 54.2 Hz, 2H) ppm; ^{13}C NMR: δ = 14.0, 21.1, 39.2, 61.1, 108.4 (t, $^3J_{CF}$ = 5.7 Hz), 108.9 (t, $^1J_{CF}$ = 239.5 Hz), 128.0, 129.2, 137.1, 137.2 (t, $^2J_{CF}$ = 22.0 Hz), 141.9, 165.1 ppm; ^{19}F NMR: δ = −121.5 (d, J = 54.2 Hz, 2F), −121.8 (d, J = 54.2 Hz, 2F) ppm; HRMS (EI) for $C_{20}H_{21}F_4NO_4$, calcd:

415.1407, found: 415.1346.

*Diethyl 2,6-bis(difluoromethyl)-4-(4-bromophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3c**)*

Yield 70%, white solid, mp 85.9–86.8 °C. ^{1}H NMR: δ= 1.26 (t, J = 7.1 Hz, 6H), 4.13–4.22 (m, 4H), 5.06 (s, 1H), 7.05 (s, 1H), 7.16 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.42 (t, J_{HF} = 54.2 Hz, 2H) ppm; ^{13}C NMR: δ= 14.0, 39.4, 61.3, 107.9 (t, $^3J_{CF}$ = 5.7 Hz), 108.8 (t, $^1J_{CF}$ = 239.7 Hz), 121.4, 129.8, 131.6, 137.6 (t, $^2J_{CF}$ = 22.2 Hz), 143.7, 164.8 ppm; ^{19}F NMR: δ= −121.6 (d, J = 54.2 Hz, 2F), −121.7 (d, J = 54.2 Hz, 2F) ppm; HRMS (EI) for $C_{19}H_{18}BrF_4NO_4$, calcd: 479.0355, found: 479.0357.

*Diethyl 2,6-bis(difluoromethyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3d**)*

Yield 73%, white solid, mp 81.8–82.1 °C. ^{1}H NMR: δ= 1.26 (t, J = 7.1 Hz, 6H), 3.78 (s, 3H), 4.12–4.21 (m, 4H), 5.07 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.02 (s, 1H), 7.19 (d, J = 8.6 Hz, 2H), 7.42 (t, J_{HF} = 54.3 Hz, 2H) ppm; ^{13}C NMR: δ= 14.0, 38.8, 55.2, 61.1, 108.6 (t, $^3J_{CF}$ = 5.7 Hz), 109.0 (t, $^1J_{CF}$ = 240.8 Hz), 113.8, 129.2, 137.1 (t, $^2J_{CF}$ = 22.0 Hz), 158.9, 165.1 ppm; ^{19}F NMR: δ= −121.5 (d, J = 54.3 Hz, 2F), −121.7 (d, J = 54.3 Hz, 2F) ppm; HRMS (EI) for $C_{20}H_{21}F_4NO_5$, calcd: 431.1356, found: 431.1359.

*Diethyl 2,6-bis(difluoromethyl)-4-(4-fluorophenyl)-1-dihydropyridine-3,5-dicarboxylate (**3e**)*

Yield 65%, white solid, mp 81.5–82.0 °C. ^{1}H NMR: δ= 1.25 (t, J = 7.1 Hz, 6H), 4.13–4.22 (m, 4H), 5.07 (s, 1H), 7.02 (s, 1H), 6.94–7.26 (m, 4H), 7.42 (t, J_{HF} = 54.4 Hz, 2H) ppm; ^{13}C NMR: δ= 14.0, 39.0, 61.2, 108.2 (t, $^3J_{CF}$ = 5.6 Hz), 108.9 (t, $^1J_{CF}$ = 239.6 Hz), 115.2 (d, J = 21.3 Hz), 129.6 (d, J = 8.0 Hz), 137.4 (t, $^2J_{CF}$ = 22.1 Hz), 140.6, 160.8, 163.3, 164.8 ppm; ^{19}F NMR: δ= −114.9– −115.0 (m, 1F), −121.6 (d, J = 54.3 Hz, 2F), −121.7 (d, J = 54.3 Hz, 2F) ppm; HRMS (EI) for $C_{19}H_{18}F_5NO_4$, calcd: 419.1156, found: 419.1157.

*Diethyl 2,6-bis(difluoromethyl)-4-(3-cyanophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3f**)*

Yield 75%, white solid, mp 141.3–142.7 °C. ^{1}H NMR: δ= 1.25 (t, J = 7.0 Hz, 6H), 4.13–4.21 (m, 4H), 5.13 (s, 1H), 7.15 (s, 1H), 7.38–7.56 (m, 6H) ppm; ^{13}C NMR: δ= 14.0, 39.7, 61.5, 107.4 (t, $^3J_{CF}$ = 5.6 Hz), 108.7 (t, $^1J_{CF}$ = 241.5 Hz), 112.5, 118.7, 129.5, 131.1, 131.8, 132.6, 138.1 (t, $^2J_{CF}$ = 22.3 Hz), 146.1, 164.5 ppm; ^{19}F NMR: δ= −121.6 (s, 2F), −121.7 (s, 2F) ppm; HRMS (EI) for $C_{20}H_{18}F_4N_2O_4$, calcd: 426.1203, found: 426.1205.

*Diethyl 2,6-bis(difluoromethyl)-4-(4-bromo-2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3g**)*

Yield 65%, white solid, mp 88.7–89.0 °C. ^{1}H NMR: δ= 1.24 (t, J = 7.2 Hz, 6H), 4.12–4.20 (m, 4H), 5.51 (s, 1H), 7.10 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.34–7.54 (m, 4H) ppm; ^{13}C NMR: δ= 14.1, 37.1, 61.3, 107.7 (t, $^3J_{CF}$ = 5.6 Hz), 108.7 (t, $^1J_{CF}$ = 241.3 Hz), 121.5, 130.7, 132.2, 132.6, 133.5, 137.9 (t, $^2J_{CF}$ = 22.2 Hz), 142.1, 164.8 ppm; ^{19}F NMR: δ= −121.9 (s, 2F), −121.0 (s, 2F) ppm; HRMS (EI) for $C_{19}H_{17}BrClF_4NO_4$, calcd: 514.6932, found: 514.9946.

*Diethyl 2,6-bis(difluoromethyl)-4-(2,3-difluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3h**)*

Yield 68%, white solid, mp 112.0–113.7 °C. ^{1}H NMR: δ= 1.23 (t, J = 7.2 Hz, 6H), 4.13–4.16 (m, 4H), 5.42 (s, 1H), 7.00–7.11 (m, 4H), 7.43 (t, J_{HF} = 54.4 Hz, 2H) ppm; ^{13}C NMR: δ= 13.7, 33.9, 61.3, 106.9 (t, $^3J_{CF}$ = 5.6 Hz), 108.6 (t, $^1J_{CF}$ = 239.7 Hz), 116.1 (d, J = 17.4 Hz), 124.1 (dd, J_1 = 4.8 Hz, J_2 = 6.6 Hz), 125.4, 134.8 (d, J = 11.0 Hz), 138.2 (t, $^2J_{CF}$ = 22.2 Hz), 149.1 (dd, J_1 = 13.2 Hz, J_2 = 30.1 Hz), 151.7 (d, J = 13.6 Hz), 164.7 ppm; ^{19}F NMR: δ = −122.1 (s, 2F), −122.3 (s, 2F), −138.9 (d, J = 18.7 Hz, 1F), −141.4 (d, J = 20.6 Hz, 1F) ppm; HRMS (EI) for $C_{19}H_{17}F_6NO_4$, calcd: 437.1062, found: 437.1063.

*Diethyl 2,6-bis(difluoromethyl)-4-(4-chloro-2-(trifluoromethyl) phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3i**)*

Yield 76%, white solid, mp 88.6–89.4 °C. ^{1}H NMR: δ= 1.22 (t, J = 7.1 Hz, 6H), 4.05–4.28 (m, 4H), 5.71 (s, 1H), 7.10 (s, 1H), 7.24–7.56 (m, 5H) ppm; ^{13}C NMR: δ= 13.8, 35.3 (q, J = 3.7 Hz), 61.4, 108.8 (t, $^1J_{CF}$ = 241.2 Hz), 109.0 (t, $^3J_{CF}$ = 5.6 Hz), 122.6 (q, J = 275.3 Hz),127.1 (q, J = 5.1 Hz), 128.6 (q, J = 31.1 Hz), 132.7, 132.9, 133.8, 137.7 (t, $^2J_{CF}$ = 22.3 Hz), 142.3, 164.8 ppm; ^{19}F NMR: δ= −56.1 (s, 3F), −121.7 (d, J = 54.1 Hz, 2F), −121.9 (d, J = 54.1 Hz, 2F) ppm; HRMS (EI) for $C_{20}H_{17}ClF_7NO_4$, calcd: 503.0734, found: 503.0737.

*Diethyl 2,6-bis(difluoromethyl)-4-propyl-1,4-dihydropyridine-3,5-dicarboxylate (**3j**)*

Yield 70%, oil. ^{1}H NMR: δ = 0.87 (t, J = 7.1 Hz, 3H), 1.22–1.40 (m, 10H), 4.05 (t, J = 5.7 Hz, 1H), 4.21–4.31 (m, 4H), 7.03 (s, 1H), 7.36 (t, J_{HF} = 54.3 Hz, 2H) ppm; ^{13}C NMR: δ= 13.9, 14.1, 17.6, 33.1, 38.0, 61.0, 107.9 (t, $^3J_{CF}$ = 5.7 Hz), 108.8 (t, $^1J_{CF}$ = 240.2 Hz), 138.5 (t, $^2J_{CF}$ = 22.0 Hz), 165.4 ppm; ^{19}F NMR: δ= −121.3 (d, J = 54.3 Hz, 2F), −121.4 (d, J = 54.3 Hz, 2F) ppm; HRMS (EI) for $C_{16}H_{21}F_4NO_4$, calcd: 367.1407, found: 367.1408.

*Diethyl 2,6-bis(difluoromethyl)-4-ethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3k**)*

Yield 70%, oil. ^{1}H NMR: δ= 0.84 (t, J = 7.5 Hz, 3H), 1.35 (t, J = 7.1 Hz, 6H), 1.44–1.51 (m, 2H), 4.04 (t, J = 5.4 Hz, 1H), 4.21–4.36 (m, 4H), 7.01 (s, 1H), 7.40 (t, J_{HF} = 54.3 Hz, 2H) ppm; ^{13}C NMR: δ= 8.7, 14.1, 28.4, 34.4, 61.0, 107.3 (t, $^3J_{CF}$ = 5.6 Hz), 108.8 (t, $^1J_{CF}$ = 240.2 Hz), 138.6 (t, $^2J_{CF}$ = 22.0 Hz), 165.4 ppm; ^{19}F NMR: δ= −121.2 (d, J = 54.3 Hz, 2F), −121.3 (d, J = 54.3 Hz, 2F) ppm; HRMS (EI) for $C_{15}H_{19}F_4NO_4$, calcd: 353.1250, found: 353.1261.

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