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Synthesis of 1, 4- Dihydropyrano [2, 3-c] pyrazole Derivatives with no Catalyst Under Ultrasound Irradiation

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Abstract: A series of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1, 4-dihydropyrano [2, 3-c]pyrazoles were synthesized in 84%-95% yields by the condensation of aromatic aldehydes, malononitrile with 3-methyl-1-phenyl-2-pyrazolin -5-one with no catalyst under ultrasound irradiation.

Key words: pyrano[2, 3-c] pyrazole, 3-methyl-1-phenyl-2-pyrazolin-5-one, aromatic aldehydes, synthesis

Introduction

Recently, 4*H*-benzo-pyran derivatives have attracted strong interest because of their useful biological and pharmacological activities, such as anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactin.¹ Some 2-amino-4*H*-pyrans can be employed as photoactive materials.² Furthermore, multisubstitutional 4*H*-pyrans also constitute a structural unit of some natural products.³ In addition, substituted pyrazole and derivatives can be used as important pharmaceuticals and agricultural chemicals. Usually these compounds were synthesized by classical

methods.⁴⁻⁵ Microwave has been used to synthesize 4*H*-benzo-pyran⁶ in shorter reaction time, using piperidine as catalyst. But, these methods suffer from drawbacks such as longer reaction times, high temperatures, or necessary catalysts.

Ultrasound irradiation has increasingly been used in organic synthesis in recent years. Compared with traditional methods, this method is more convenient and easily controlled. A large number of organic reactions can be carried out in higher yield, shorter reaction time and milder conditions under ultrasound irradiation⁷. Herein, we would like to report the synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1, 4- dihydropyrano [2, 3-*c*] pyrazoles (4) through the condensation of aromatic aldehydes (1), malononitrile(2) with 3-methyl-1-phenyl-2-pyrazolin-5-one (3) under ultrasound irradiation (**scheme 1**).

Scheme 1. Synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1, 4-dihydropyrano [2, 3-*c*] pyrazoles

Experimental

Materials and Measurements

Liquid aldehydes were purified by distillation prior to use. Melting points were uncorrected. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ¹H NMR spectra were measured on a Bruker AVANCE (400 MHz) spectrometer using TMS as an internal standard and CDCl₃ as a solvent. Elemental analysis measured on a HERAEUS (CHN, Rapid) analyzer. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner with a frequency of 25 KHz and a nominal power 250W. The reaction flasks were located in the maximum energy area in the cleaner, where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

General Procedure

Aromatic aldehyde 1(1 mmol), malononitrile 2(1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one 3(1 mmol) and EtOH (5 mL) were mixed in a 50 mL tapered Pyrex flask. The mixture was irradiated in the water bath of the ultrasonic cleaner at the room temperature. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water (20 mL) and the resulting solid was filtered. The collected solid was washed with water and then recrystallized from EtOH/CHCl₃ to afford pure products. All the products were confirmed by comparing their melting points, IR and ¹H NMR data with literature data.

4c: IR (KBr) $\nu_{\max}$: 3463, 3319, 2193, 1655, 1594, 1391, 1070, 756 cm^{-1} ; ^1H NMR δ : 1.93 (s, 3H, CH_3), 4.67(s, 1H, 4-H), 4.74(s, 2H, NH_2), 7.19-7.37(m, 5H, ArH), 7.48(d, 2H, $J=8.0\text{Hz}$, ArH), 7.67(d, 2H, $J=8.0\text{Hz}$, ArH). Found: C 66.01, H 4.05, N 15.41. Calc. for $\text{C}_{20}\text{H}_{15}\text{ClN}_4\text{O}$: C 66.21, H 4.17, N 15.44.

4d: IR (KBr) $\nu_{\max}$: 3472, 3324, 2194, 1655, 1591, 1389, 1264, 1125, 1029, 752 cm^{-1} ; ^1H NMR δ : 1.91 (s, 3H, CH_3), 4.73(s, 2H, NH_2), 5.32(s, 1H, 4-H), 7.21-7.43(m, 5H, ArH), 7.48(d, 2H, $J=8.0\text{Hz}$, ArH), 7.67(d, 2H, $J=8.0\text{Hz}$, ArH). Found: C 66.11, H 4.08, N 15.61. Calc. for $\text{C}_{20}\text{H}_{15}\text{ClN}_4\text{O}$: C 66.21, H 4.17, N 15.44.

4e: IR (KBr) $\nu_{\max}$: 3456, 3321, 2198, 1660, 1591, 1392, 1269, 1126, 1049, 758 cm^{-1} ; ^1H NMR δ : 1.78 (s, 3H, CH_3), 5.12(s, 1H, 4-H), 6.73(s, 2H, NH_2), 7.31-7.78(m, 8H, ArH). Found: C 66.35, H 3.40, N 14.33. Calc. for $\text{C}_{20}\text{H}_{14}\text{Cl}_2\text{N}_4\text{O}$: C 60.47, H 3.55, N 14.10.

4f: IR (KBr) $\nu_{\max}$: 3072, 2908, 2258, 1612, 1528, 1412, 1194, 1107, 857, 752 cm^{-1} ; ^1H NMR δ : 2.12 (s, 3H, CH_3), 4.90(s, 2H, NH_2), 5.22(s, 1H, 4-H), 7.22-8.30(m, 9H, ArH). Found: C 64.40, H 3.12, N 18.80. Calc. for $\text{C}_{20}\text{H}_{15}\text{N}_5\text{O}_3$: C 64.34, H 3.05, N 18.76.

4i: IR (KBr) $\nu_{\max}$: 3414, 3314, 2179, 1657, 1593, 1399, 1257, 1127, 1026, 753 cm^{-1} ; ^1H NMR δ : 1.78 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.62(s, 1H, 4-H), 6.96(s, 2H, NH_2), 7.02 (d, 2H, $J=8.4\text{Hz}$, ArH), 7.08 (d, 2H, $J=8.4\text{Hz}$, ArH), 7.29-7.33(m, 1H, ArH), 7.46 (d, 2H, $J=8.0\text{Hz}$, ArH), 7.78 (d, 2H, $J=8.0\text{Hz}$, ArH). Found: C 73.52, H 5.19, N 16.25. Calc. for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}$: C 73.67, H 5.30, N 16.36.

4k: IR (KBr) $\nu_{\max}$: 3414, 3314, 2179, 1657, 1593, 1399, 1257, 1127, 1026, 753 cm^{-1} ; ^1H NMR δ : 1.79 (s, 3H, CH_3), 4.56(s, 1H, 4-H), 6.72 (d, 2H, $J=8.4\text{Hz}$, ArH), 7.04 (d, 2H, $J=8.4\text{Hz}$, ArH), 7.12(s, 2H, NH_2), 7.29-7.33(m, 1H, ArH), 7.49 (d, 2H, $J=8.0\text{Hz}$, ArH), 7.78 (d, 2H, $J=8.0\text{Hz}$, ArH). Found: C 69.54, H 4.35, N 15.93. Calc. for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_2$: C 69.76, H 4.68, N 16.27.

4l: IR (KBr): $\nu_{\max}$: 3400, 3320, 2198, 1661, 1595, 1393, 1254, 1129, 1037, 789 cm^{-1} ; ^1H NMR δ : 2.12 (s, 3H, CH_3), 5.09(s, 1H, 4-H), 5.95(2H, s, OCH_2O), 6.92(s, 2H, NH_2), 7.02-7.12(m, 2H, ArH), 7.15(m, 1H, ArH), 7.17(d, 2H, $J=8.0\text{Hz}$, ArH), 7.21(m, 1H, ArH), 7.26(d, 2H, $J=8.0\text{Hz}$, ArH). Found: C 67.51, H 4.28, N 15.26. Calc. for $\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}_3$: C 67.73, H 4.33, N 15.05.

Results and Discussion

The results are summarized in **Table 1**. It can easily be seen that the condensation of 1, 2 with 3 in EtOH gives 4 in good yields under ultrasound irradiation with no catalyst.

As shown in **Table 1**, the reaction of 1, 2 with 3 were carried out in 3~30min and give 4 in 84%~95% yields using ethanol as solvent under ultrasound irradiation with no catalyst. We found that all aldehydes carrying electron-withdrawing (1f~1h) or weak electron-donating substituents (1a~1e, 1i) reacted with 2 and 3 very well at room temperature under ultrasound irradiation, gave corresponding products in good yields. However, these aldehydes carrying strong electron-donating substituents (1j~1l) need longer time to finish the reaction. In addition, this reaction was affected by steric effect. The reaction need more time when aldehydes are 2-substituted (such as 1d~1f).

We proposed the possible mechanism to account for the reaction (described as **Scheme 2**). One molecule of 1 was firstly condensed with 2 to afford α -cyanocinnamionitrile derivative (5). The step (1+2 $\rightarrow$ 5) could be regarded as a fast Knoevenagel reaction. The active methylene of 3 reacted with the electrophilic C=C double bond of 5 to give the intermediate (6). Then the intermediate 6 was cyclized by the nucleophilic attack of OH group on the cyano (CN) and gave the intermediate 7. Finally the expected products 4 were afforded (7 $\rightarrow$ 8 $\rightarrow$ 4).

Table 1. Condensation of aromatic aldehydes, malononitrile with 3-methyl-1-phenyl-2-pyrazolin-5-one in EtOH with no catalyst under ultrasound irradiation

Entry	Ar	Time/min	Yield ^a /%	M.p./°C(Lit.)
a	C ₆ H ₅	5	84	167-169(168-170) ⁶
b	4-ClC ₆ H ₄	3	95	172-174(174-175) ⁶
c	3-ClC ₆ H ₄	8	91	157-158
d	2-ClC ₆ H ₄	15	94	145-146
e	2,4-Cl ₂ C ₆ H ₄	10	92	182-184
f	2-NO ₂ C ₆ H ₄	20	87	157-158
g	3-NO ₂ C ₆ H ₄	5	90	187-189(188-190) ⁶
h	4-NO ₂ C ₆ H ₄	3	87	193-195(194-196) ⁶
i	4-CH ₃ C ₆ H ₄	5	86	176-178
j	4-OCH ₃ C ₆ H ₄	20	89	169-170(170-172) ⁶
k	4-OHC ₆ H ₄	30	93	214-215
l	3,4-OCH ₂ OC ₆ H ₃	25	90	175-176

^aIsolated yield, based on aldehydes. **Scheme 2.** The possible mechanism of the reaction

Conclusion

In conclusion, we have described a simple and efficient procedure for the preparation of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano [2, 3-c]pyrazoles in EtOH with no catalyst under ultrasound irradiation.

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