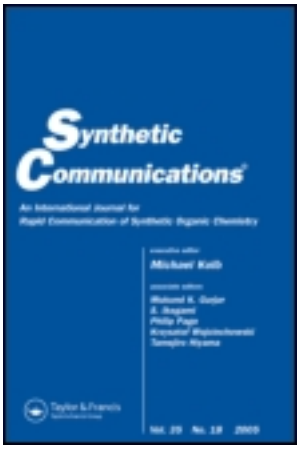

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TETRAKIS(ACETONITRILE)COPPER(I) HEXAFLUOROPHOSPHATE–PROMOTED EFFICIENT SYNTHESIS OF AMIDOALKYL NAPHTHOLS UNDER SOLVENT-FREE CONDITIONS

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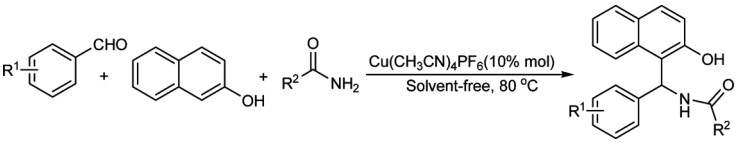
GRAPHICAL ABSTRACT



Abstract *An efficient and direct protocol for the preparation of amidoalkyl naphthols employing a multicomponent, one-pot condensation reaction of β-naphthol, aromatic aldehydes, and amides (acetamide, benzamide, and urea) in the presence of tetrakis(acetonitrile)copper(I) hexafluorophosphate [$Cu(CH_3CN)_4PF_6$] under solvent-free conditions at 80 °C is described. Good yields, short reaction time, and easy workup are advantages of this procedure.*

Keywords Amidoalkyl naphthols; $Cu(CH_3CN)_4PF_6$; multicomponent reaction; β-naphthol; solvent-free

INTRODUCTION

Multicomponent reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion.[1] Devising types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis.[2] As such processes avoid time-consuming and costly purification processes, as well as protection–deprotection steps, they are inherently more environmentally benign and atom economic.[3] They provide a powerful tool for one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles.[4]

1-Amidoalkyl-2-naphthols are important intermediates that can be easily converted into biologically active 1-aminoalkyl-2-naphthols derivatives by amide hydrolysis.[5] The classical method for synthesis of 1-amidoalkyl-2-naphthols

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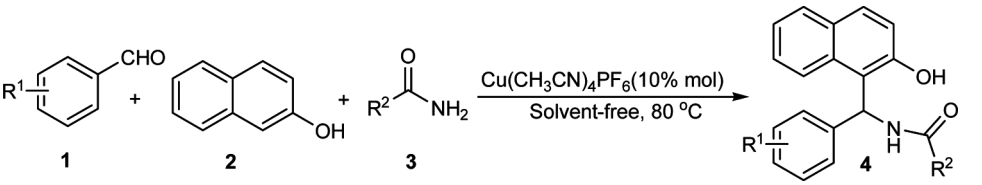

Scheme 1. Synthesis of amidoalkyl naphthols in the presence of $Cu(CH_3CN_4)PF_6$ catalyst.

involves the condensation of aryl aldehydes, β-naphthol, and an amide in the presence of Lewis or Brønsted acid catalysts such as such as *para*-toluene-sulfonic acid (p-TSA),[6] montmorillonite K10,[7] $Ce(SO_4)_2$,[8] iodine,[9] $Fe(HSO_4)_3$,[10] $Sr(OTf)_2$,[11] $K_5CoW_{12}O_{40} \cdot 3H_2O$,[12] sulfamic acid,[13] molybdophosphoric acid,[14] cation-exchange resins,[15] silica sulfuric acid,[16] indium(III) chloride,[17] and ionic liquid.[18] However, some of the reported methods suffer from disadvantages such as prolonged reaction time, poor yield of products, toxic and corrosive reagents, and the use of additional microwave or ultrasonic irradiation.

In continuation of our work to develop new synthetic methodologies,[19] herein we report a new, convenient, mild, and efficient procedure for one-pot, three-component synthesis of amidoalkyl naphthol derivatives **4** from various aryl aldehydes **1**, β-naphthol **2**, and different amides **3** (acetamide, benzamide, and urea) in the presence of $Cu(CH_3CN)_4PF_6$ as an effective catalyst under solvent-free conditions at 80 °C (Scheme 1).

$Cu(CH_3CN)_4PF_6$ is a free-flowing, white, microcrystalline powder that does not darken on long-term storage in an inert atmosphere. Exposure to air for longer than about 1 h results in minor surface oxidation as a result of the slightly hygroscopic nature of the complex. The complex is moderately soluble in polar solvents and is remarkably stable to air oxidation in CH_3CN solution.[20]

RESULTS AND DISCUSSION

To study the feasibility of the $Cu(CH_3CN)_4PF_6$ catalysis in this reaction, the reaction of benzaldehyde, β-naphthol, and acetamide was selected as a model under solvent-free conditions.

We first studied the model reaction catalyzed by $Cu(CH_3CN)_4PF_6$ (10 mol%) at different temperatures. The reaction rate was increased as the reaction temperature was raised. When it was carried out at 80 °C, the maximum yield was obtained in a short reaction period. Next, to evaluate the effect of catalyst concentration, the model reaction was carried out in the presence of different amounts of catalyst (5, 10, 15, 20 and 25 mol%) at 80 °C. The result showed that 10 mol% of catalyst was sufficient to achieve a fairly good yield. The results of using $Cu(CH_3CN)_4PF_6$ as a catalyst in the reaction of various aldehydes, β-naphthol, and various amides are summarized in Table 1. Various functionalities present in the aryl aldehydes such as halogen, hydroxy, methyl, and nitro groups in amides such as acetamide, benzamide, and urea were tolerated. In all these cases, the corresponding amidoalkyl naphthols were obtained in good yields.

To show the merit of the present work in comparison with reported results in the literature, we compared results of $Cu(CH_3CN)_4PF_6$ with p-TSA,[6] $Ce(SO_4)_2$,[8]

Table 1. Preparation of 1-amidoalkyl-2-naphthols

Entry	R^1	R^2	Time (min)	Yield (%)	Mp (°C) Found	Mp (°C) Reported
1	H	CH_3	60	93	238–240	241–243[8]
2	4-NO_2	CH_3	45	94	246–248	248–250[10]
3	3-NO_2	CH_3	35	90	238–240	241–242[10]
4	3-OH	CH_3	20	98	236–238	—
5	4-OH	CH_3	65	75	205–207	—
6	4-Cl	CH_3	70	78	218–221	223–225[8]
7	2-Cl	CH_3	80	75	212–214	213–215[15]
8	2,4-Cl	CH_3	35	80	197–200	198–199[8]
9	4-CH_3	CH_3	70	97	221–223	222–223[10]
10	H	NH_2	15	75	169–172	172–174[12]
11	3-NO_2	NH_2	27	89	180–182	184–186[12]
12	4-Cl	NH_2	30	90	162–164	168–169[12]
13	4-Cl	C_6H_5	56	77	175–177	177–178[12]
14	3-NO_2	C_6H_5	50	75	214–216	216–217[12]

iodine,[9] and $K_5CoW_{12}O_{40} \cdot 3H_2O$[12] in the synthesis *N*-[(3-nitro phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide from 3-nitro benzaldehyde, acetamide, and 2-naphthol. As shown in Table 2, $Cu(CH_3CN)_4PF_6$ can act as effective catalyst with respect to reaction times, yields, and simplified conditions.

CONCLUSION

In conclusion, we have developed a simple and efficient synthesis of amidoalkyl naphthols using $Cu(CH_3CN)_4PF_6$ catalyst under solvent-free conditions. This method offers some advantages in terms of simplicity of performance, short reaction times, good yields, and solvent-free condition, and it follows the line of green chemistry. This protocol could serve as a valuable alternative to known reaction systems.

EXPERIMENTAL

$Cu(CH_3CN)_4PF_6$ (0.037 g, 0.1 mmol) was added to a mixture of 2-naphthol (1 mmol), aldehydes (1 mmol), and acetamide (1.2 mmol). The mixture was stirred at 80 °C in an oil bath and the reaction was followed by thin-layer chromatography (TLC). After completion, the mixture was cooled to 25 °C, dichloromethane was

Table 2. Comparison of the efficiencies of various catalysts used in the synthesis of amidoalkyl naphthols

Catalyst	Conditions/Temp. (°C)	Time	Yield (%)	Reference
p-TSA	Solvent-free/125	5 h	88	6
$Ce(SO_4)_2$	Under reflux	16 h	65	8
I_2	Solvent-free/125	5 h	81	9
$K_5CoW_{12}O_{40} \cdot 3H_2O$	Solvent-free/120	3 h	78	12
$Cu(CH_3CN)_4PF_6$	Solvent-free/80	35 min	90	This work

added, and the mixture stirred for 5 min. Products were filtered and recrystallized from aqueous ethanol.

All the products (except entries 4 and 5) are known compounds, which were characterized by IR and ^{1}H NMR spectral data, and their melting points were compared with literature reports.

N-((2-Hydroxynaphthalen-1-yl)(3-hydroxyphenyl)methyl)acetamide (Entry 4)

White powder (0.30 g, yield 98%); mp 236–238 °C. IR (KBr) (ν_{max}/cm^{-1}): 3456, 1612, 1539, 1443. MS, m/z (%): 307 (M^+, 20), 247 (50), 230 (100), 115 (20). ^{1}H NMR (200 MHz, DMSO-d_6): δ_H (ppm) = 1.98 (3H, s, CH_3), 6.57–7.83 (11H, m, H-Ar and C*H*-N*H*), 8.41 (1H, d, $^3J_{HH}$ = 8.3 Hz, H-Ar), 9.22, 10.00 (2H, 2 s, 2OH). ^{13}C NMR (50 MHz, DMSO-d_6): δ_C (ppm) = 22.35 (CH_3), 47.35 (*C*H-NH), 112.80, 116.43, 118.14, 118.60, 122.09, 123.08, 125.96, 128.20, 128.63, 128.84, 132.08, 143.85, 152.81, 156.83 (C-Ar), 168.91 (C=O). Anal. calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.30; H, 5.55; N, 4.63.

N-((2-Hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methyl)acetamide (Entry 5)

White powder (0.23 g, yield 75%); mp 205–207 °C. IR (KBr) (ν_{max} /cm^{-1}): 3408, 1609, 1510, 1430. MS, m/z (%): 307 (M^+, 20), 247 (50), 230 (100), 202 (15), 115 (20). ^{1}H NMR (200 MHz, DMSO-d_6): δ_H (ppm) = 1.93 (3H, s, CH_3), 6.61–8.37 (12H, m, H-Ar and C*H*-N*H*), 9.18, 9.93 (2H, 2 s, 2OH). ^{13}C NMR (50 MHz, DMSO-d_6): δ_C (ppm) = 22.41 (CH_3), 47.17 (*C*H-NH), 114.46, 118.19, 118.78, 122.03, 123.00, 125.88, 126.97, 128.18, 128.68, 131.99, 132.22, 152.69, 155.37 (C-Ar), 169.00 (C=O). Anal. calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.30; H, 5.55; N, 4.63.

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