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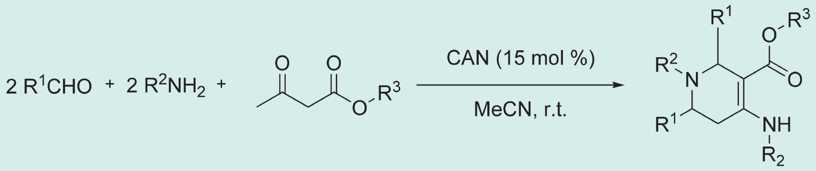
Cerium Ammonium Nitrate-Catalyzed Multicomponent Reaction for Efficient Synthesis of Functionalized Tetrahydropyridines

Hong-Juan Wang, Li-Ping Mo, and Zhan-Hui Zhang*

The College of Chemistry & Material Science, Hebei Normal University, Shijiazhuang 050016, China

Supporting Information

ABSTRACT: A highly atom-economic one-pot synthesis of functionalized tetrahydropyridines by a multicomponent condensation reaction of β-keto ester, two equivalents of aromatic aldehyde, and two equivalents of amine in the presence of a catalytic amount of cerium ammonium nitrate (CAN) is reported. In this way, a series of pharmacologically interesting substituted piperidine derivatives were obtained in moderate to good yields at room temperature.



KEYWORDS: multicomponent reaction, one-pot, cerium ammonium nitrate, tetrahydropyridines, heterocycles

INTRODUCTION

Multicomponent coupling reactions (MCRs) represent a highly valuable synthetic tool for the construction of novel and complex molecular structures with a minimum number of synthetic steps. These types of reactions have some advantages over conventional linear syntheses, including lower costs, shorter reaction times, high degrees of atom economy, the possibility for combinatorial surveying of structural variations, and environmental friendliness. Among notable recent efforts to develop new MCRs,[1] Bonfield et al. recently reported an efficient method for the preparation of the isoindoline framework via a six-component, tandem double A3-coupling and [2+2+2]-cycloaddition reaction.[2] Brauch et al. have extended MCRs to seven components by taking advantage of the different chemoselectivities of the Ugi−Mumm and the Ugi−Smiles reaction.[3] Recently, the Orru group developed a one-pot reaction of up to eight components that involves nine new bond formations and eleven points of diversity.[4] In this content, MCRs that involve 1,3-dicarbonyl compounds, aldehydes, and nucleophilic compounds have received much attention in recent years because the formation of different condensation products can be expected depending on the specific conditions and structures of the building blocks.

The tetrahydropyridine ring is an essential building block for numerous natural products, synthetic pharmaceuticals, and a wide variety of biologically active compounds.[5] (See Supporting Information for a list of activities and references.) As a consequence, the development of general methods for the synthesis of tetrahydropyridine derivatives has been the subject of considerable synthetic efforts and still requires attention. Most current procedures either require advanced starting materials or involve multistep and low-yielding reaction sequences. Among the more successful are a proline-mediated cascade Mannich-type/intramolecular cyclizations,[6] a palladium-catalyzed alkynyl and allenyl iminium ion cyclizations,[7] phosphine-promoted [3+3]-annulations of aziridines with allenoates,[8] and radical cyclization of *N*-allylamino-substituted Baylis−Hillman adducts.[9]

One-pot, multicomponent reactions offer potential advantages.[10] Of the many approaches to the synthesis of tetrahydropyridines, the atom and step economic (PASE)[11] synthesis of functionalized tetrahydropyridines from relatively simple starting materials is especially attractive. Recently, one-pot syntheses of these heterocyclic compounds by condensation reactions employing $InCl_3$,[12] L-proline/TFA,[13] bromodimethylsulfonium bromide,[14] and tetrabutylammonium tribromide (TBATB)[15] have been reported. However, in these limited cases high loadings (up to 33 mol %)[12] of expensive catalysts[13] were necessary to achieve reasonably high yields. The development of simple and environmentally benign synthetic methods for efficient preparation of functionalized tetrahydropyridines is therefore a significant challenge.

In recent years, cerium ammonium nitrate (CAN) has been employed as a multipurpose promotor of a wide range of synthetically useful reactions.[16] However, most examples require stoichiometric quantities of CAN. We report herein a highly atom-economic synthesis of functionalized tetrahydropyridines by a one-pot, three (in situ five)-component reaction requiring CAN in only 15 mol % (Scheme 1).

RESULTS AND DISCUSSION

Various potential catalysts were tested for the direct synthesis of **4c** by the model reaction of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) in acetonitrile at room temperature, with results listed in Table 1. CAN

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Scheme 1. CAN Catalyzed Synthesis of Tetrahydropyridines

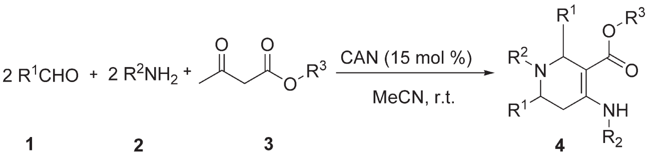
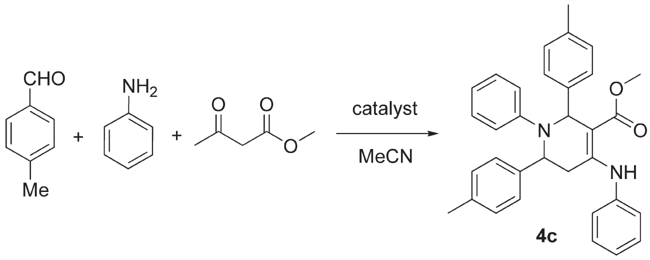


Table 1. Effect of Different Catalysts on the Model Reaction of 4-Methylbenzaldehyde, Aniline, and Methyl Acetoacetate[a]



entry	catalyst	reaction time (h)	yield (%)[b]
1	none	30	trace
2	$HClO_4/SiO_2$	50	60
3	*p*-toluenesulfonic acid	50	58
4	phosphotungstic acid	50	65
5	$(NH_4)_3PMo_{12}O_{40}\cdot 6H_2O$	50	41
6	$Mg(ClO_4)_2$	50	40
7	$LiClO_4\cdot 3H_2O$	50	35
8	$ZrOCl_2\cdot 8H_2O$	50	45
9	$ZrO(NO_3)_2$	50	72
10	$Co(NO_3)_2\cdot 6H_2O$	50	68
11	$(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$	50	42
12	CAN	22	85

[a] Experimental conditions: 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), and catalyst (0.15 mmol) in 5 mL of MeCN at room temperature. [b] Isolated yields.

Table 2. Investigation of the Amounts of Catalyst and Solvent Effects on the Model Reaction of Table 1[a]

entry	catalyst loading (mol %)	solvent	time (h)	yield (%)[b]
1	15	EtOAc	46	50
2	15	EtOH	40	75
3	15	THF	47	70
4	15	H_2O	50	28
5	10	MeCN	35	70
6	15	MeCN	22	85
7	20	MeCN	22	86

[a] Experimental conditions: 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), and CAN in 5 mL of solvent at room temperature. [b] Isolated yields.

proved to be superior, producing the best yield of **4c**, only trace amounts of which were formed in the absence of catalyst (Table 1, entry 1).

A survey of solvents revealed acetonitrile to be the best choice, used directly without rigorous drying. Low yields were obtained when EtOAc or water was employed as the solvent. Some dependence was also observed on the amount of CAN used. A satisfactory result was obtained in the presence of 15 mol % CAN (Table 2, entry 6), with no improvement upon increasing the catalyst loading to 20 mol %.

The scope and limitations of this five-component reaction under optimized conditions were explored using a variety of aldehydes, amines, and β-keto esters, as summarized in Table 3. In general, aromatic aldehydes bearing electron-donating or electron-withdrawing functional groups at different positions reacted with methyl acetoacetate smoothly in the presence of aniline to generate the corresponding products in good to excellent yields. In contrast, aliphatic aldehydes such as *n*-hexanal and cyclohexanecarboxaldehyde did not provide the desired products. Aromatic amines were found to be effective substrates and afforded the corresponding tetrahydropyridine derivatives in high yields. Aliphatic amines gave moderate yields (Table 3, entries 44−47), presumably due to the higher basicity of aliphatic amines compared to anilines. Lastly, other β-keto esters such as ethyl acetoacetate, *iso*-butyl acetoacetate, *tert*-butyl acetoacetate, allyl acetoacetate, and 2-methoxyethyl acetoacetate were examined. The alkoxy ($-OR^3$) moiety present had little influence on the reaction, and generally good yields were obtained. Benzoyl acetone (**5**) also proved to be an excellent substrate, giving good yields of the corresponding products (Scheme 2).

The products were characterized by IR, ^1H NMR, and ^{13}C NMR spectra and by elemental analysis. The stereochemistry of the products **4** with 2- and 6-substituents on the six-membered ring of tetrahydropridine was determined as trans by single-crystal X-ray analysis (see the Supporting Information, Figure 1).

A proposed reaction mechanism for this five-component reaction is outlined in Scheme 3. CAN can serve as a Lewis acidic catalyst for the reaction of aniline and methyl acetoacetate or 4-chlorobenzaldehyde to give the β-enaminone[17] or imine,[16a] respectively. The intermolecular Mannich addition of the β-enaminone (**7**) to the imine (**8**) affords the intermediate **9**. Subsequently, the reaction of activated aldehyde with the intermediate **9** proceeds to afford the intermediate **10** by the elimination of H_2O. Intermediate **10** should tautomerize to provide **11**, stabilized by intramolecular hydrogen bonding. Intramolecular Mannich addition gives intermediate **12**, which finally transformes to the expected piperidine tautomer **4c**. CAN may enhance the rates of several of these transformations. This scheme is supported by two principal experimental observations: (1) the reaction intermediates **7** and **8** could be isolated in the course of reaction, and (2) the reaction of **7**, **8**, and 4-methylbenzaldehyde gave the same product as the reaction of methyl acetoacetate, 4-methylbenzaldehyde, and aniline.

In conclusion, we have developed an efficient synthesis of functionalized tetrahydropyridines suitable for combinatorial synthesis through a one-pot, five-component reaction using a catalytic amount of CAN at room temperature. The attractive features of this procedure are the mild reaction conditions, high atom efficiency, clean reaction profiles, inexpensive starting materials, and an environmentally friendly catalyst.

Table 3. CAN-Catalyzed Synthesis of Functionalized Tetrahydropyridines

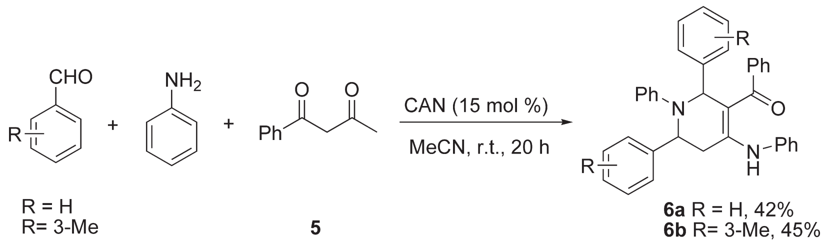
entry	R^1	R^2	R^3	products	time (h)	yield (%)[a]	mp (°C)	
							found	reported
1	Ph	Ph	Me	**4a**	20	82	194−195	194[13]
2	3-$CH_3C_6H_4$	Ph	Me	**4b**	23	84	131−134	89.3−90.2[12]
3	4-$CH_3C_6H_4$	Ph	Me	**4c**	22	85	215−216	212−214[14]
4	2-$OCH_3C_6H_4$	Ph	Me	**4d**	30	80	248−251	
5	4-$OCH_3C_6H_5$	Ph	Me	**4e**	16	83	182−183	180[13]
6	3,4,5-$(OMe)_3C_6H_2$	Ph	Me	**4f**	30	73	156−158	153−156[14]
7	4-FC_6H_4	Ph	Me	**4g**	20	81	161−162	160[13]
8	3-ClC_6H_4	Ph	Me	**4h**	24	75	220−221	220[13]
9	4-ClC_6H_4	Ph	Me	**4i**	15	86	225−226	225−227[18]
10	4-BrC_6H_4	Ph	Me	**4j**	16	84	245−246	245−247[13]
11	2-$NO_2C_6H_4$	Ph	Me	**4k**	20	75	232−234	217−219[14]
12	3-$NO_2C_6H_4$	Ph	Me	**4l**	19	80	181−182	180[13]
13	4-$NO_2C_6H_4$	Ph	Me	**4m**	18	78	240−241	239−241[14]
14	3-$CF_3C_6H_4$	Ph	Me	**4n**	45	80	140−142	
15	Ph	4-$OCH_3C_6H_4$	Me	**4o**	20	82	224−225	223.5−224.1[12]
16	3-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	Me	**4p**	18	81	193−194	193.5−194.5[12]
17	4-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	Me	**4q**	17	75	226−227	225−226[14]
18	4-FC_6H_4	4-$OCH_3C_6H_4$	Me	**4r**	17	82	204−205	205[13]
19	3-ClC_6H_4	4-$OCH_3C_6H_4$	Me	**4s**	17	80	162−163	160[13]
20	4-ClC_6H_4	4-$OCH_3C_6H_4$	Me	**4t**	17	75	214	
21	4-BrC_6H_4	4-$OCH_3C_6H_4$	Me	**4u**	16	83	179−180	179[13]
22	3-$CF_3C_6H_4$	4-$OCH_3C_6H_4$	Me	**4v**	22	80	157−158	156.2−157.2[12]
23	3-$CH_3C_6H_4$	Ph	${}^{i}Bu$	**4w**	23	62	140−142	
24	3-$CH_3C_6H_4$	Ph	${}^{t}Bu$	**4x**	23	81	154−155	
25	3-$CH_3C_6H_4$	Ph	$CH_2CH{=}CH_2$	**4y**	24	56	157−159	
26	3-$CH_3C_6H_4$	Ph	CH_2CH_2OMe	**4z**	23	85	140−142	
27	Ph	Ph	Et	**4aa**	23	80	175−176	174−175[14]
28	Ph	Ph	${}^{t}Bu$	**4ab**	23	78	162−163	162−163[14]
29	Ph	Ph	$CH_2CH{=}CH_2$	**4ac**	24	60	150−151	149−150[14]
30	Ph	4-$OCH_3C_6H_4$	Et	**4ad**	20	82	172−173	173[13]
31	Ph	4-ClC_6H_4	Et	**4ae**	35	68	201−202	202[13]
32	4-$CH_3C_6H_4$	Ph	Et	**4af**	23	78	230−231	227−230[14]
33	4-$CH_3C_6H_4$	Ph	${}^{t}Bu$	**4ag**	23	81	170−171	171−173[18]
34	4-$CH_3C_6H_4$	Ph	$CH_2CH{=}CH_2$	**4ah**	24	66	175−176	172−174[14]
35	4-$NO_2C_6H_4$	Ph	Et	**4ai**	20	75	247−250	
36	4-$CH_3C_6H_4$	4-BrC_6H_4	Me	**4aj**	28	67	253−254	253−254[14]
37	4-BrC_6H_4	4-ClC_6H_4	Me	**4ak**	28	69	159−160	160−163[13]
38	4-$OCH_3C_6H_4$	4-ClC_6H_4	Me	**4al**	21	65	194−195	195[13]
39	4-$OCH_3C_6H_4$	4-BrC_6H_4	Me	**4am**	21	68	177−178	178[13]
40	4-FC_6H_4	4-ClC_6H_4	Me	**4an**	22	75	175−176	176[13]
41	4-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	Et	**4ao**	22	81	221−224	
42	3-ClC_6H_4	4-$OCH_3C_6H_4$	Et	**4ap**	20	83	168−169	167−170[13]
43	3-ClC_6H_4	4-ClC_6H_4	Et	**4aq**	25	82	189−190	190[13]
44	4-$CH_3C_6H_4$	$PhCH_2$	Me	**4ar**	40	52	172−173	172−173[14]
45	4-$CH_3C_6H_4$	$CH_3(CH_2)_3$	Me	**4as**	40	51	155−156	153−154[14]
46	3-$CH_3C_6H_4$	$CH_3(CH_2)_2$	Me	**4at**	40	53	151−153	
47	3-$CH_3C_6H_4$	$CH_3(CH_2)_3$	Me	**4au**	40	55	144−146	

[a] Isolated yields.

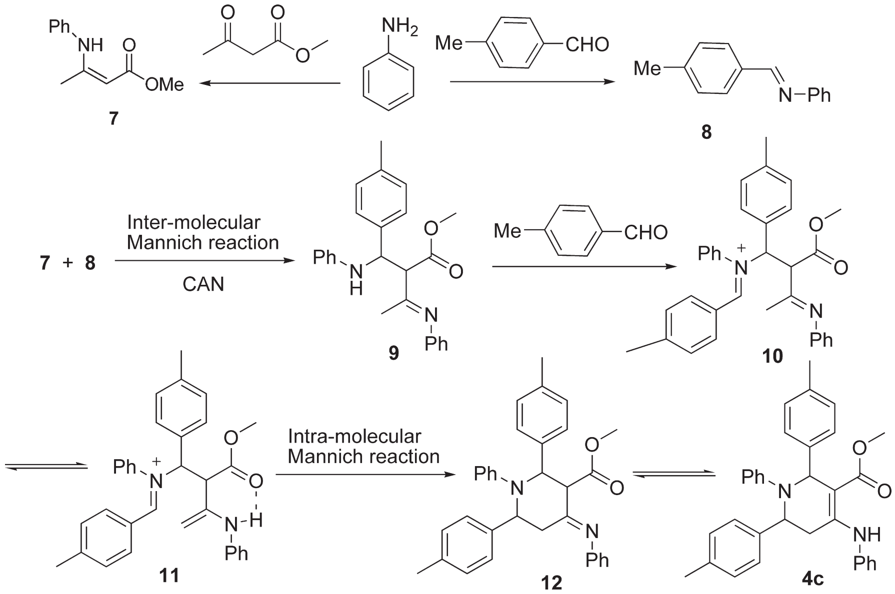
■ EXPERIMENTAL PROCEDURES

General Procedure for the Preparation of Functionalized Tetrahydropyridines (4). A mixture of β-keto ester (1.0 mmol), aldehyde (2.0 mmol), amine (2 mmol), and CAN (0.15 mmol) in 5 mL of acetonitrile was stirred at room temperature for an appropriate time (Table 3). After completion of the reaction, as indicated by TLC,

Scheme 2. Reaction of Aldehyde, Aniline, and Benzoyl Acetone Catalyzed by CAN



Scheme 3. Proposed Mechanistic Steps for the Multicomponent Synthesis of Tetrahydropyridines



the mixture was diluted with ethyl acetate (20 mL), washed with water and then brine, and dried with anhydrous Na_2SO_4. The filtrate was concentrated and purified by silica gel column chromatography.

ASSOCIATED CONTENT

Supporting Information. Experimental procedure, spectroscopic characterization for compound **4**, and the X-ray crystallographic information for compound **4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone: 86 311 86263124. Fax: 86 311 89632795. E-mail: zhanhui@mail.nankai.edu.cn.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Structure 7 of Scheme 3 was modified in the version of this paper published December 16, 2010. The correct version published January 7, 2011.