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Chloroacetic acid-promoted heterocyclic reactions: Efficient preparation of tetrahydropyridines and 2,3-dihydroquinazolin-4(1H)-ones

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ABSTRACT

Facile and versatile procedures have been explored for the synthesis of tetrahydropyridines and 2,3-dihydroquinazolin-4(1*H*)-ones. These protocols employ the one-pot multi-component condensation of arylaldehydes and aromatic amines with β-keto esters and isatoic anhydride in chloroacetic acid, respectively. The reactions proceeded smoothly to generate the corresponding products in high yield. We have found that the use of chloroacetic acid as catalyst results in a remarkable beneficial effect on the reaction, allowing it to be performed without the need of any co-catalyst, which is the case in other similar reported methodologies. In addition, the preparation of 2,3-dihydro-4(1*H*)-quinazolinones derivatives from the reaction of arylaldehydes and anthranilamide in the presence of mentioned catalyst is reported.

***Keywords**: Tetrahydropyridines, 2,3-Dihydroquinazolin-4(1H)-ones, Multi-component reaction, Mild conditions.*

1. Introduction

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as an effective method to generate molecular diversity [1-3]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [4,5]. 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 [6]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [7]. Of the more than 20 million chemical compounds currently registered, about one half contain heterocyclic systems. Heterocycles are important, not only because of their abundance, but also because of their chemical, biological, and technical significances.

Heterocycles count among their number many natural products, such as vitamins, hormones, antibiotics, alkaloids, as well as pharmaceuticals, herbicides, and dyes [8]. In connection with our previous work on multi component reaction using convenient and inexpensive acid as a catalyst [9] we wish to report a simple but effective procedure for the synthesis of tetrahydropyridines and 2,3-dihydroquinazolin-4(1*H*)-ones by employing chloroacetic acid as a sort of efficient catalyst. We also investigated two component reaction of arylaldehydes or arylketones and anthranilamide for prapration 2,3-dihydro-4(1*H*)-quinazolinones deriveties using mentioned catalyst (Scheme 1).

2. Experimental

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer respectively. The ^{1}HNMR spectra were obtained from a BRUKER DRX-400 AVANCE instrument with $CDCl_3$ as a solvent. All reagents and solvents were obtained from Fluka and used without further purification.

2.1. General procedure for the synthesis of tetrahydropyridines

To a magnetically stirred solution of amine (2.0 mmol), β-keto ester (1.0 mmol) and Cl_3CCO_2H

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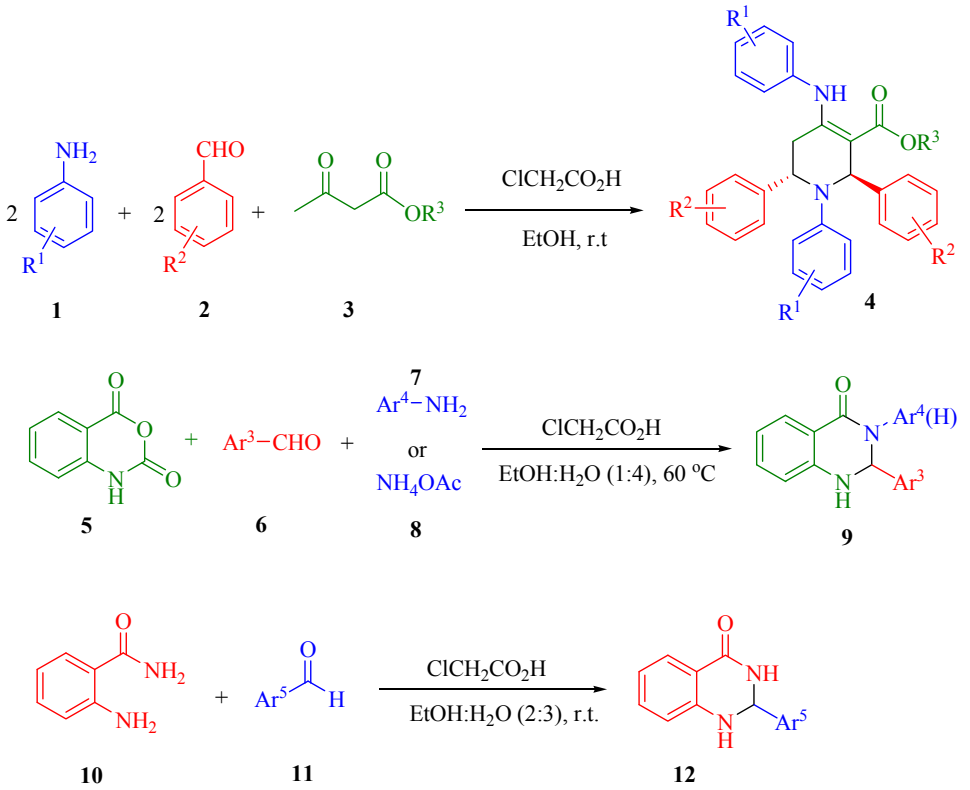


Scheme 1. Synthesis of high functionalized tetrahydropyridines and 2,3-dihydroquinazolin-4(1*H*)-ones in presence of chloroacetic acid.

(0.11 g) in 3 mL of EtOH, after 20 min, aromatic aldehyde (2.0 mmol) was added and stirred at room temperature. Stirring was continued for completion. The progress of the reaction was monitored by TLC. After completion of the reaction, the thick precipitate was filtered off and washed with ethanol to give pure products.

2.2. General Procedure for the Synthesis of 2,3-disubstituted-2,3-Dihydroquinazolin-4(1H)-ones

To a mixture of isatoic anhydride (1.0 mmol), aromatic aldehyde (1.0 mmol), and amine in water/ethanol (4:1), chloroacetic acid (0.020 g) was added and the reaction mixture was stirred at 60 °C for an appropriate period of time. After completion of the reaction, which was indicated by TLC, water was added, and the mixture was cooled to room temperature. The precipitated product was filtered off and finally recrystallized from ethanol.

2.3. General Procedure for the synthesis of 2-Substituted-2,3-Dihydroquinazolin-4(1H)-ones

2-aminobenzamide (1.0 mmol) and aldehyde or ketone (1.0 mmol) was successively added to a solution of catalyst (0.01 g) in water and ethanol in the ratio of (3:2) at room temperature. The progress of the reaction is monitored by TLC. After completion of the reaction, the reaction mixture was filtered by addition of water and ethanol to afford the crude product. Then the crude product was purified by recrystallized from ethanol.

Selected Spectral data

Compound (***4j***):

^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.51 (3H, t, *J*=7.2 Hz, OC-CH_3), 2.81 (1H, dd, *J*= 15.2,2.4 Hz, H'-5), 2.92 (1H, dd, *J*= 14.8, 5.2 Hz, H"-5), 4.34-4.42 (1H, m, OCH_aH_b), 4.47-4.55 (1H, m, OCH_aH_b), 5.19 (1H, d, *J*= 3.6 Hz, H-6), 6.32 (2H, d, *J*= 8.0 Hz, ArH), 6.51 (1H, s, H-2), 6.57 (2H, d, *J*= 8.0 Hz, ArH), 6.65 (1H, t, *J*= 7.2 Hz, ArH), 7.09-7.40 (15H, m, ArH), 10.34 (1H, s, NH) ppm.

Compound (***4o***)**:**

^{1}HNMR (400 MHz, $CDCl_3$): δ= 2.91, 2.92 (2H, 2s, H', H"-5), 4.00 (3H, s, OCH_3), 5.31 (1H, s, H-6), 6.42-8.20 (19H, m, H-2, ArH), 10.32 (1H, s, NH) ppm.

3. Results and discussion

In order to carry out the preparation of tetrahydropyridines in a more efficient way minimizing the time and amount of catalysts, the reaction of 4-methylbenzaldehyde (2.0 mmol), aniline (2.0 mmol) and ethylacetoacetate (1.0 mmol) was selected as a model system. The different amount of

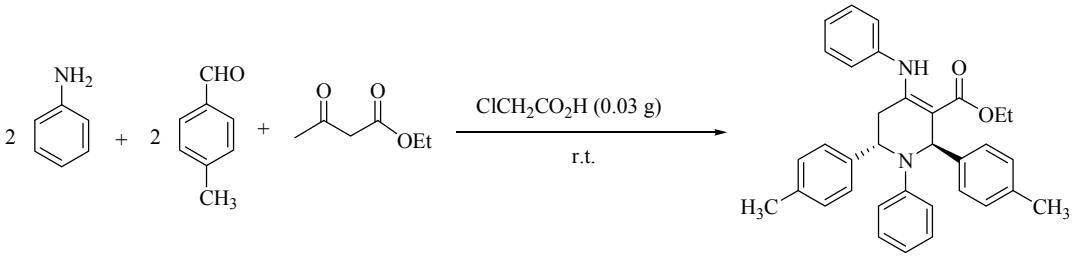
chloroacetic acid as catalysts in different solvent was investigated. The best result was obtained with chloroacetic acid (0.11g) in ethanol (3 mL) under ambient conditions (Table 1 and 2).

Using this optimized reaction, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted tetrahydropyridines derivatives (Table 3). Interestingly, a variety of arylaldehydes including electron withdrawing or releasing substituents (*meta*-, and *para*-substituted) participated well in this reaction and gave the desired products in good to excellent yield.

According to the literature survey [9] the suggested mechanism for the formation of the products is shown in Scheme 2. Chloroacetic acid results in the formation of enamine A and imine B (Scheme 2.). It is well known that enamine A would be a better nucleophile and the nucleophilic attack would preferentially take place on the activated imine B to give intermediate C through an intermolecular Mannich-type reaction. The intermediate C reacts with aldehyde to give intermediate D by the elimination of a H_2O molecule. There is a spontaneous tendency in the presence of chloroacetic acid for tautomerization to give the intramolecular hydrogen bonded species either E or F. The tautomer F immediately undergoes intramolecular Mannich-type reaction to form intermediate G. The intermediate G tautomerizes to give the final tetrahydropyridines derivatives.

In order to show the accessibility of the present work in comparison with the reported results in the literature [9-14], we showed that chloroacetic acid was an efficient catalyst with respect to the reaction time and obtained product yield (Table 3).

Table 1. The solvent effect on catalytic function of chloroacetic acid (0.03 g) in the synthesis of (2R, 6S) ethyl 1, 2, 5, 6-tetrahydro-1-phenyl-4-(phenylamino)-2, 6-dip-tolyl pyridine-3-carboxylate.



Entry	Solvent	Isolated Yield (%)
1	Ethanol	58
2	Methanol	55
4	Ethyl acetate	37
5	Acetonitrile	25
6	No solvent	30

Table 2. Investigation of amount of chloroacetic acid as a catalyst for the synthesis of (2R, 6S) ethyl 1, 2, 5, 6-tetrahydro-1-phenyl-4-(phenylamino)-2, 6-dip-tolyl pyridine-3-carboxylate.

Entry	Catalyst (g)	Isolated Yield (%)
1	0.01	46
2	0.03	58
3	0.05	62
4	0.07	68
5	0.09	78
6	0.10	82
7	0.11	85
8	0.12	85

Table 3. Synthesis of tetrahydropyridine derivatives.

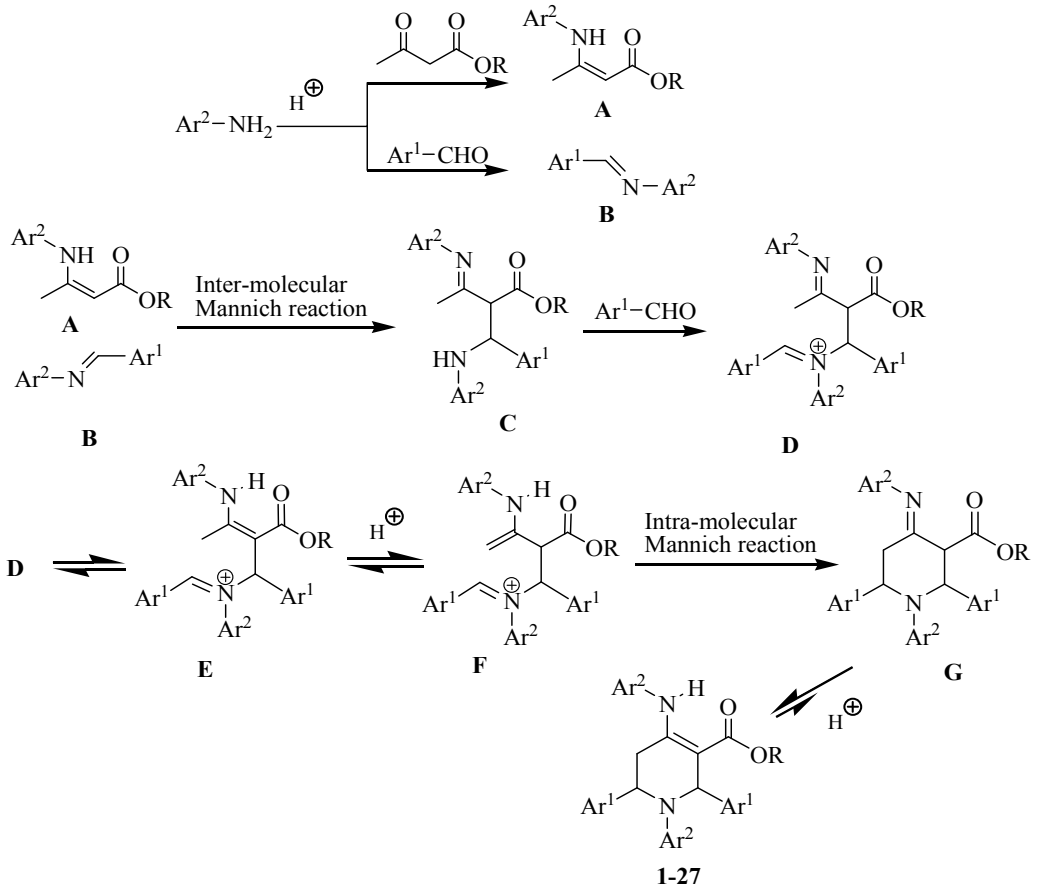
Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	m.p. (°C)		Ref.
							Found	Reported	
1	4-Me	H	Me	4a	2	86	213-215	215-217	[10]
2	4-Me	H	Et	4b	5	85	228-230	228-231	[10]
3	4-Me	4-Br	Me	4c	4	90	229-233	230-232	[10]
4	4-Me	4-OMe	Me	4d	3	70	224-227	225-226	[11]
5	4-Me	4-OMe	Et	4e	4	83	218-220	221-224	[12]
6	4-Me	4-Me	Me	4f	9	69	200-204	206-208	[10]
7	4-Me	4-F	Et	4g	11	61	184-186	183-185	[13]
8	4-Me	3,4-$(Cl)_2$	Et	4h	5	75	174	173-175	[13]
9	H	H	Me	4i	7	82	169-173	169-171	[11]
10	H	H	Et	4j	5	75	176-177	174-175	[11]
11	H	4-Br	Et	4k	4	83	200-202	196-198	[14]
12	H	4-OMe	Et	4l	3	87	178-180	179-181	[13]
13	4-Cl	H	Me	4m	10	87	184-188	189-191	[11]
14	3-Br	H	Et	4n	4	75	165	164-167	[9]
15	4-NO_2	H	Me	4o	11	51	236-238	239-241	[10]
16	3-NO_2	H	Me	4p	11	54	181-183	178-181	[13]
17	H	4-Cl	Et	4q	3	85	201-203	198-201	[13]
18	4-NO_2	H	Et	4r	9	71	247-248	247-250	[12]

[a]Yields refer to the isolated pure products. The desired pure products were characterized by comparison of their physical data (melting points, IR, ^{1}H NMR) with those of known compounds.

In continuation of our research on application of mentioned catalyst, we tried to synthesis 2,3-dihydroquinazolin-4(1*H*)-ones derivatives in a more efficient way by minimizing the time, temperature and amount of catalyst.

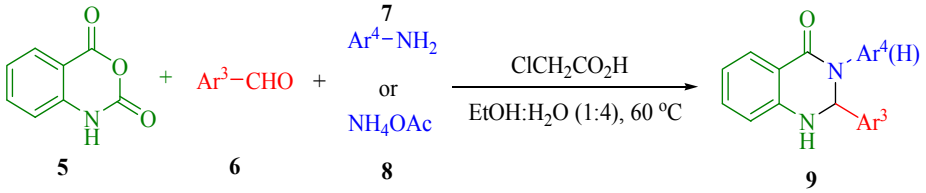
The reaction of benzaldehyde (1.0 mmol), aniline (1.0 mmol) and isatoic anhydride (1.0 mmol) was selected as a model system and the catalyst activity at different temperatures (r.t , 40, 60, 80 and 100°C) and different amounts of catalyst (0.005, 0.010, 0.020, 0.030, 0.040 and 0.050 g) were investigated. The best result was obtained with chloroacetic acid (0.020 g) at 60°C in the mixture of EtOH-H_2O (1:4). Next, three-component condensation reaction of aromatic aldehydes, aniline and isatoic anhydride under optimized conditions for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives were investigated. Different aldehydes were converted to the corresponding products in high to excellent yields using chloroacetic acid as a catalyst (Table 4).

We also investigated the preparation of 2,3-dihydro-4(1*H*)-quinazolinones deriveties from the reaction of arylaldehydes or arylketones and anthranilamide. We optimized the amount of catalyst and solvent in the two component reaction between arylaldehydes or arylketones (1.0 mmol) and anthranilamide



Scheme 2. Proposed mechanism for synthesis of highly functionalized tetrahydropyridines.

Table 4. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives.



Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)[a]	m.p. (°C)		Ref.
						Found	Reported	
1	Ph	Ph	9a	5	75	206-208	207	[15]
2	4-ClC_6H_4	Ph	9b	4.5	71	219-221	216	[15]
3	Ph	4-ClC_6H_4	9c	4.5	78	218-219	215	[15]
4	4-ClC_6H_4	4-ClC_6H_4	9d	3.5	70	255-257	250	[16]
5	4- $O_2NC_6H_4$	Ph	9e	6	89	192-193	195	[15]
6	3- $O_2NC_6H_4$	ph	9f	6.5	82	187-189	186	[15]
7	4-MeC_6H_4	Ph	9g	4.5	77	209-210	205	[15]
8	4-ClC_6H_4	NH_4OAc	9h	8	47	202-203	198	[17]
9	Ph	NH_4OAc	9i	8	63	223-225	219	[17]

[a]Yields refer to the isolated pure products. The desired pure products were characterized by comparison of their physical data (melting points, IR, ^{1}H NMR) with those of known compounds.

(1.0 mmol). The best result was obtained with chloroacetic acid (0.010 g) in EtOH:H_2O (2:3) in ambient conditions. Next, two-component condensation reaction of aromatic aldehydes (and cyclohexanone) and anthranilamide under optimized conditions for preparation of 2,3-dihydro-4(1*H*)-quinazolinones deriveties derivatives were investigated (Table 5,6). A number of substituted and structurally diverse aldehydes and anilines were reacted to form the corresponding products in high to excellent yields chloroacetic acid as catalyst (Table 7).

To show the merit of the present work in comparison with reported results in the literature, we compared results of chloroacetic acid with iodine [10], bromodimethylsulfonium bromide (BDMS) [11], cerium ammonium nitrate (CAN) [12], *p*-TsOH.H_2O [13], and oxalic acid dihydrate [14] in the synthesis of tetrahydropyridine derivatives. As shown in Table 8, chloroacetic acid can act as effective catalyst with respect to reaction times and yields of products.

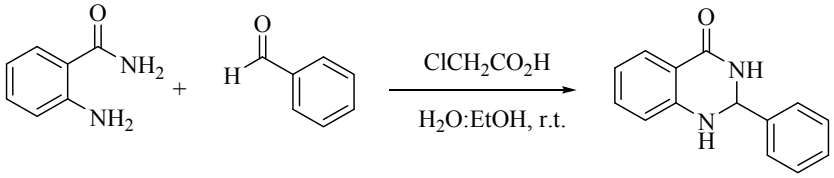
4. Conclusion

In summary, mild and efficient methods for the synthesis of highly functionalizaed tetrahydropyridines and 2,3-dihydro-4(1*H*)-quinazolinone derivatives in the presence of chloroacetic acid as an inexpensive catalyst, from commonly available starting materials have been developed. In all cases, the products can be collected easily by filtration.

Acknowledgment

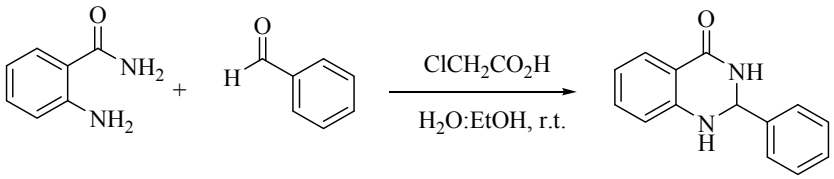
We are thankful to the University of Sistan and Baluchestan Research Council for the partial support of this research.

Table 5. Optimization of solvent for the synthesis of 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one.



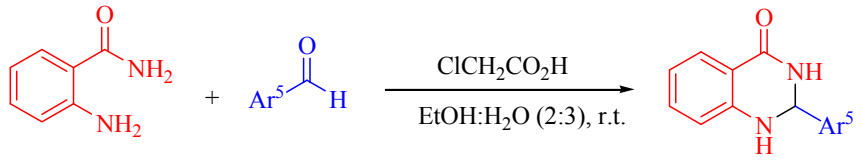
Entry	Solvent (H_2O:EtOH)	Time (min)	Isolated Yield (%)
1	1:1	20	96
2	2:3	20	91
3	3:2	20	99
4	4:1	20	90
5	1:4	20	88

Table 6. Optimization of the catalyst amount for the synthesis of 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one.



Entry	Catalyst (g)	Time (min)	Isolated Yield (%)
1	0.010	20	99
2	0.020	20	98
3	0.030	20	97
4	0.040	20	88
5	0.050	20	89

Table 7. Synthesis of 2,3-dihydro-4(1*H*)-quinazolinone derivatives.



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Entry	Aldehyde or Ketone	Product	Time (min)	Yield (%)[a]	m.p. (°C)		Ref.
					Found	Reported	
1	C_6H_5CHO	12a	20	90	225-228	225-226	[18]
2	4-$CH_3C_6H_4CHO$	12b	35	91	204-206	205-206	[19]
3	3,4-$(CH_3O)_2C_6H_3CHO$	12c	15	88	210-212	208-212	[20]
4	4-$(CH_3)_2NC_6H_4CHO$	12d	30	97	215-216	212-214	[21]
5	4-ClC_6H_4CHO	12e	45	90	181-184	181-185	[22]
6	2,4-$(Cl)_2C_6H_3CHO$	12f	20	75	208-210	203-205	[23]
7	2-ClC_6H_4CHO	12g	50	95	224-227	224-225	[21]
8	Cyclohexanone	12h	60	87	225-227	224-226	[24]

[a]Yields refer to the isolated pure products. The desired pure products were characterized by comparison of their physical data (melting points, IR, ^{1}HNMR) with those of known compounds.

Table 8. Comparison result of chloroacetic acid with previously reported catalyst for the synthesis of tetrahydropyridine **4a**.

Catalyst/Conditions	Time (h)	Yield (%)	Ref.
I_2 / MeOH, r.t.	8	84	[10]
BDMS / CH_3CN, r.t.	10	78	[11]
CAN / CH_3CN, r.t.	22	85	[12]
p-TsOH.H_2O / EtOH, r.t.	7	89	[13]
Oxalic acid dihydrate / EtOH, r.t.	12	81	[14]
Chloroacetic acid / EtOH, r.t.	2	86	This work

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