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Diketene-based neat four-component synthesis of the dihydropyrimidinones and dihydropyridine backbones using silica sulfuric acid (SSA)

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Abstract

Heterocyclic skeleton building blocks to afford dihydropyrimidinones and dihydropyridines based on neat adducts of diketene, alcohols and aldehydes *via* silica sulfuric acid (SSA) catalyzed ring opening of diketene in four-component Biginelli-type and Hantzsch-type reactions are presented.

Keywords: Diketene; Dihydropyrimidinone; Dihydropyridine; Heterocyclic skeleton; Silica sulfuric acid

1. Introduction

Dihydropyrimidinones (DHPMs) and dihydropyridines (DHPs) are found to exhibit a wide spectrum of biological activities [1,2]. However a number of the reported protocols to synthesize DHPMs [3] and DHPs [4] in high yields requiring solvents and catalysts such as heavy metals are not acceptable in the context of costs or green catalyst. The developments in this area demand further searches for neat methods and diversity in reagents that could be superior to the existing ones with regard to generality, simplicity, high yields and handling. In other hand, after introduction of the silica sulfuric acid (SSA) as a useful heterogeneous solid acid by Zolfigol in 2001, many research papers have been published on its application in organic synthetic methodology and multicomponent reactions [5]. In this respect, we are interested in presenting potential neat diketene, alcohols and aldehydes adduct for preparation of the DHPMs and DHPs heterocyclic skeleton to overcome these limitations in presence of silica sulfuric acids (SSAs). In this new heterogeneous neat method which is based on using diketene as original, *in situ* source of variable β-ketoesters in four-component synthesis of DHPMs and DHPs is described. The neat approach, easiness and variability in derivatives of the present four-component procedure make it an interesting alternative to three-component approaches.

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2. Experimental

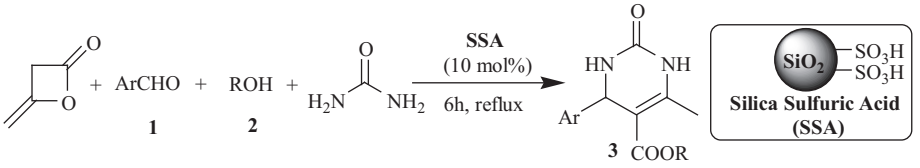
To a magnetically stirred of equivalent amount of neat adduct diketene (1 mmol) and aldehyde (1 mmol) and alcohol in excess amount of equivalent (4 mL) in SSA (10 mol%) for 5 min at reflux condition, urea or ammonium acetate (1.2 mmol) was added, and then heated in neat state with stirring in refluxing condition, for an appropriate time (TLC monitoring). After that hot ethanol (20 mL) was added and the mixture was filtered to remove the catalyst. The reaction was cooled to room temperature and the solid was washed with cooled water, petroleum ether/ether. All the products were previously reported and were characterized by comparing physical data with those. Spectral data for selected products: methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**). M.P. 207–211 (207–210). IR (KBr): 3325, 3316, 1698, 1661, 1585, 1422. ^{1}H NMR (300.1 MHz, $CDCl_3$): 2.35 (3, s, CH_3), 3.62 (3, s, OCH_3), 5.40 (1, d, *J* 2.1 Hz, C*H*NH), 5.53 (1, br, NH), 7.25–7.33 (5, m, C_6H_5), 7.56 (1, br, NH). Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4d**). M.P. 150–153 (154–159). IR (KBr): 3345, 1703, 1657, 1473, 1198, 1130. ^{1}H NMR (300.1 MHz, $CDCl_3$): 1.20 (6, t, *J* 7.0 Hz, OCH_2CH_3), 2.31 (6, s, CH_3), 4.09 (4, q, *J* 7.0 Hz, OCH_2CH_3), 5.01 (1, s, CH), 6.20 (1, s, NH), 7.10–7.39 (5, m, C_6H_5).

3. Result and discussion

Although the three-component synthesis of DHPMs and DHPs *via* Biginelli and Hantzsch condition has been studied [3,4,8,9]. To our surprise, one-pot reaction between diketene, urea, and aldehydes in presence of SSA as a heterogeneous catalyst and methanol as solvent, produced Biginelli product dihydropyrimidin-2(1*H*)-ones, methanol is main partial of heterocycle skeleton in this reaction. So, based on this founding, in a new plan in heterocycle synthesis, we explored the potential neat adduct of diketene/alcohols/aldehydes for four-component condensation of this adduct with NH_4OAc and urea at reflux condition. Recently, we have reported and developed the multicomponent heterocyclic skeleton synthesis such as DHPMs, DHPs [6], rhodanine, furans and others [7] herein we wish to report a simple and potential DHPMs and DHPs heterocycle synthesis based on diketene/alcohols/aldehydes neat adduct, in the presence of SSA as a heterogeneous solid acid catalyst in one-pot four-component Biginelli-type and Hantzsch-type condensation protocols, respectively.

The neat reaction of diketene, aldehydes **1**, alcohols **2**, with urea in the presence of catalytic amount SSA underwent an Biginelli cyclocondensation reaction at refluxing condition, to produce 3,4-dihydropyrimidin-2-(1*H*)-one derivatives **3** (Table 1).

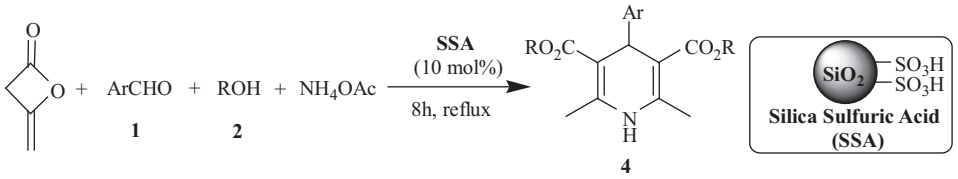
Table 1
The neat four-component synthesis of DHPMs.



	Ar	R	M.P. (°C)		%Yield[a]
			Found	Reported	
3a	C_6H_5	Me	207–211	207–210[8a]	90
3b	C_6H_5	Et	200–204	201–203[8a]	80
3c	2-Cl–C_6H_4	Me	255–257	252–253[8b]	81
3d	2-Cl–C_6H_4	Et	210–212	215–218[8a]	88
3e	3-Cl–C_6H_4	Me	210–213	208–210[3b]	88
3f	3-Cl–C_6H_4	Et	190–194	192–193[3a]	81
3g	4-Cl–C_6H_4	Me	201–203	204–207[3a]	91
3h	4-Cl–C_6H_4	Et	214–215	210–212[3a]	93
3i	4-NO_2–C_6H_4	Me	237–238	235–237[8a]	90
3j	4-NO_2–C_6H_4	Et	209–211	207–210[8a]	90

[a] Isolated and non-optimized yields.

Table 2
The neat four-component Hantzsch-type condensation of dihydropyridines.



	R	Ar	M.P. (°C)		%Yield[a]
			Found	Reported	
4a	Me	2-OMe–C_6H_4	160–162	170–171[4a]	73
4b	Me	3-OMe–C_6H_4	168–169	168–170[4a]	77
4c	Me	4-NO_2–C_6H_4	163–165	165–168[4b]	83
4d	Et	C_6H_5	150–153	154–159[9a]	87
4e	Et	2-Cl–C_6H_4	122–126	125–126[4b]	77
4f	Et	3-Cl–C_6H_4	123–124	120–121[9a]	77
4g	Et	4-Cl–C_6H_4	146–149	144–148[9a]	79
4h	Et	4-NO_2–C_6H_4	125–129	129–132[9a]	87

[a] Isolated and non-optimized yields.

The reaction was found to be general with respect to a NH_4OAc affording the 1,4-dihydropyridines (DHPs) **4** products in good yields. The results are summarized in Table 2.

4. Conclusion

In summary, we have described a simple catalitic one-pot neat synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one and 1,4-dihydropyridin derivatives *via* a four-component cyclocondensation reaction of diketene, alcohols, aldehydes with urea and NH_4OAc, respectively. In addition, the present method carries the advantage that, not only is the reaction performed under one-pot neat conditions, but also, in addition of aldehyde component, the alcohols component can be modified to synthesize derivatives, too. The retrieval, easiness and variation in derivatives in presence of heterogeneous catalitic solid acids of the present four-component procedure make it an interesting alternative to three-component approaches.

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