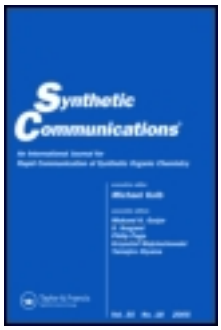

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A FACILE SYNTHESIS OF FUNCTIONALIZED 1,2,6,7-TETRAHYDROIMIDAZO[1,5-C]PYRIMIDINE-3,5-DIONES

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Abstract

A Pd-mediated hydrogenation of ethyl 6-azidomethyl-1,2,3,4-tetrahydro-4-R-2-oxo-5-pyrimidinecarboxylates leads to the corresponding ethyl 6-aminomethyl1,2,3,4-tetrahydro-4-R-2-oxo-5-pyrimidinecarboxylates. The latter react with bis(trichloromethyl)carbonate yielding the title ethyl 1,2,3,5,6,7-hexahydro-7-R-3,5-dioxoimidazo[1,5-c]pyrimidine-8-carboxylates.

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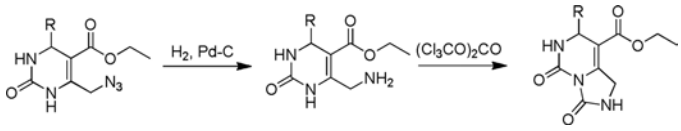

KEYWORDS: ethyl 6-azidomethyl-2-oxo-5-pyrimidinecarboxylates; ethyl 6-aminomethyl-2-oxo-5-pyrimidinecarboxylates; bis(trichloromethyl)carbonate; ethyl 3,5-dioxoimidazo[1,5-c]pyrimidine-8-carboxylates.

INTRODUCTION

The imidazo[1,5-c]pyrimidine unit, a structural analogue of purine, is found in compounds exhibiting a wide spectrum of biological activities. For example, 6-methylimidazo[1,5-c]tetrahydropyrimidine-5-thion (Zapotidine)[1,2] possesses hypnotic, sedative, and hypotensive activity. Additionally, some derivatives of imidazo[1,5-c]tetrahydropyrimidin-5-one were shown to be efficient adenosine antagonists.[3] Recently a semi-synthetic glycopeptide antibiotic containing tetrahydroimidazo[1,5-c]pyrimidine fragment was found to exhibit exceptional antibacterial activity that was higher than that of the widely used vancomycin.[4]

A most popular synthetic approach to the imidazo[1,5-c]pyrimidines consists of cyclocondensation of histamine with *N,N'*-carbonyldiimidazole,[5-11] *N,N'*-thiocarbonyldiimidazole,[12] bis(4-nitrophenyl)carbonate,[13] and *S*-phenyl ester of chlorothiocarbonic acid.[14] This methods allow a straightforward preparing of 5-oxo- or 5-thio-derivatives of imidazo[1,5-c]pyrimidines. At the same time there is a limited number of synthetic procedures for the preparation of imidazo[1,5-c]pyrimidine derivatives bearing multiple functional groups. Available examples of the multiply functionalized imidazo[1,5-c]pyrimidines include esters of imidazo[1,5-c]pyrimidine-7-cabroxylic and imidazo[1,5-c]pyrimidine-8-carboxylic acids.[15,16] It is therefore of importance to develop synthetic routes to the imidazo[1,5-c]pyrimidine derivatives bearing several functional groups serving as diversity points for the rational design of libraries of biologically potent compounds. We have recently reported[16] a convenient approach to a functionalized imidazo[1,5-c]pyrimidine system. The approach consisted of

an annulation of imidazole unit to 6-azidomethyl-5-ethoxycarbonyl-3,4-dihydropyrimidin-2-ones resulting in ethyl esters of 3-amino-5-oxotetrahydroimidazo[1,5-c]pyrimidine-8-carboxylic acids. In this contribution we improve and expand this method to prepare 3,5-dioxo-derivatives of imidazo[1,5-c]pyrimidine-8-carboxylic acids.

RESULTS AND DISCUSSION

The presented synthetic route is summarized in Scheme 1. In the first step readily available 6-azidomethyl-2-oxo-3,4-dihydropyrimidine-5-carboxylates **1a-e** are reduced into corresponding 6-aminomethyl derivatives **2a-e**. Analysis of the literature[17-20] shows that the catalytic hydrogenation under Pd/C is the most suited technique to smoothly convert various azidomethyl heterocycles into corresponding amines. The data presented in Table 1 demonstrate that in our hands the reduction was indeed successful with yields of 54-83%. Prepared compounds **2a-e**, although contain both the nucleophilic amino-group and the electrophilic ethoxycarbonyl functionality, do not undergo self-condensation under ambient conditions.[21] The annulation of imidazolidin-2-one unit in **2a-e** takes place through the reaction with bis(trichloromethyl)carbonate.[22] As depicted in Scheme 1 6-aminomethylpryrimidines **2a-e** readily react with bis(trichloromethyl)carbonate leads to ethyl 1,2,3,5,6,7-hexahydro-7-R-3,5-dioxoimidazo[1,5-c]pyrimidine-8-carboxylates **3a-e** with moderate to high yields (Table 1).

According to available literature reports on the reaction of the bis(trichloromethyl)carbonate with amines[22] the conversion of compounds **2** to **3** proceeds with displacement of bis(trichloromethyl) groups from bis(trichloromethyl)carbonate to give tetrahydroimidazo[1,5-c]pyrimidine-3,5-diones **3**. This constitutes a significant improvement of our formerly reported procedure[16] in which carbodiimide intermediates underwent cyclization in boiling chlorobenzene with low yields on account of a side reaction, that was 1,3-prototropic shift in the allyl subunit of the tetrahydroimidazopyrimidine.

^{1}H and ^{13}C NMR spectroscopy, liquid chromatography / mass spectrometry (LC/MS), and elemental analyses of compounds **2** and **3** confirmed their structural integrity and high purity.

CONCLUSIONS

An efficient and smooth approach to the novel functionalized hexahydroimidazo[1,5-c]pyrimidine derivatives was developed. The approach consists of two reaction steps occurring under mild conditions. First, the 6-azidomethylpyrimidine-2-ones are reduced catalytically to the 6-aminomethylpyrimidine-2-ones. The latter undergo cyclocondensation by treatment with bis(trichloromethyl)carbonate.

EXPERIMENTAL

Melting points were measured with Tomas Hoover apparatus and uncorrected. IR spectra were recorded on a Nexus-470 spectrophotometer in KBr tablets. ^{1}H and ^{13}C NMR

spectra were registreted in DMSO-d_6 on Bruker AVANCE DRX 500, Varian UNITY Plus 400, and Varian VRX-300 instruments with TMS as an internal standard.

Compounds **1** were synthesized according to reported procedures.[16]

General Procedure For The Preparation Of Ethyl 6-(Aminomethyl)-1,2,3,4-Tetrahydro-4-R-2-Oxo-5-Pyrimidinecarboxylates (2a-E)

The hydrogen was bubbled slowly into a stirred suspension of 6-azidomethylpyrimidine **1a-e** (0.003 mol) and 10 mol % Pd/C (100 mg) in ethanol (10 mL) over a period of 8h. Then the reaction mixture was heated to reflux and the catalyst was filtered off. The filtrate solvent was removed under reduced pressure. The solid residue was crystallized from benzene and dried in vacuum.

Ethyl 6-(aminomethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2a). IR (ν, cm^{-1}): 1705 and 1730 (C=O), 3225 and 3310 (NH), 3360 (NH_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.18 (t, 3H, J = 6.7 Hz, CH_3,), 3.64 (s, 2H, CH_2), 3.89 (s, 2H, CH_2), 4.06 (q, 2H, J = 6.7 Hz, CH_2), 7.09 (brs, 1H, NH). ^{13}C NMR (125 MHz) δ (ppm): 14.59 (CH_3), 40.65 (CH_2), 41.04 (CH_2), 59.66 (CH_2), 93.33 (C), 153.18 (C=O), 153.58 (C), 165.50 (C=O). Anal. calcd. (%) for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58; N, 21.09. Found: C, 48.43; H, 6.50; N, 21.28.

General Procedure For Preparation Of Ethyl 1,2,3,5,6,7-Hexahydro-7-R-3,5-Dioxo-Imidazo[1,5-C]Pyrimidine-8-Carboxylates (3a-E)

To a solution of bis(trichloromethyl)carbonate (1.07 g, 0.0036 mol) in dry dichloromethane (10 mL) a solution of triethylamine (1.09 g, 0.0108 mol) in dry dichloromethane (2 mL) was added dropwise at 5 °C. Then 6-aminomethylpyrimidine **2a-e** (0.0036 mol) was slowly added to the stirred reaction mixture at 5 °C. The reaction mixture was stirred at room temperature for 6h. A solid precipitate formed was filtered and washed with deionized water (25×3 mL). The crude product was crystallized from methanol and dried in vacuum.

Ethyl 3,5-dioxo-1,2,3,5,6,7-hexahydroimidazo[1,5-c]pyrimidine-8-carboxylate (3a). IR (ν, cm^{-1}): 1700 and 1765 (C=O), 3280 (NH). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.21 (t, 3H, J = 5.9 Hz, $CH_2\underline{CH_3}$), 3.94 (s, 2H, CH_2), 4.10 (m, 2H, $\underline{CH_2}CH_3$), 4.30 (s, 1H, CH_2), 7.51 (s, 1H, NH), 8.03 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 14.08 (CH_3), 40.30 (CH_2), 42.58 (CH_2), 59.91 (CH_2), 95.19 (C), 146.59 (C), 147.46 (C=O), 152.76 (C=O), 163.95 (C=O). Anal. calcd. (%) for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.71; H, 5.08; N, 18.55.

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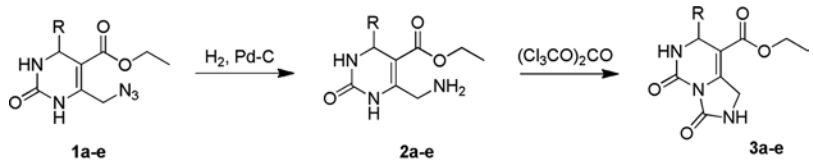
Table 1. Isolated yields and melting points of ethyl 2-oxo-5-pyrimidine-carboxylates **2a-e** and ethyl 3,5-dioxoimidazo[1,5-c]pyrimidine-8-carboxylates **3a-e**.

Entry	R	Yield (%)	Mp (°C)	Entry	R	Yield (%)	Mp (°C)
2a	H	54	161-162	3a	H	63	212-213
2b	Me	75	162-163	3b	Me	58	216-217
2c	Ph	80	166-167	3c	Ph	70	226-227
2d	4-ClC_6H_4	56	159-160	3d	4-ClC_6H_4	61	218-219
2e	4-$MeOC_6H_4$	83	153-154	3e	4-$MeOC_6H_4$	76	237-238

Scheme 1. Synthetic pathway for the preparation of ethyl 1,2,3,5,6,7-hexahydro-7-R-3,5-dioxoimidazo[1,5-c]pyrimidine-8-carboxylates **3a-e**.



a R = H;

b R = Me;

c R = Ph;

d R = 4-ClC_6H_4;

e R = 4-$MeOC_6H_4$