http://dx.doi.org/10.5935/0103-5053.20130070
J. Braz. Chem. Soc., Vol. 24, No. 4, 580-584, 2013.
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0103 - 5053 $6.00+0.00

Article

A Straightforward and Efficient Synthesis of 3-(Pyrimidinyl)propanoates from Levulinic Acid

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Neste trabalho, a ciclocondensação dos precursores 7,7,7-trifluoro-4-metoxi-6-oxo-4 heptenoato de metila e 7,7,7-trichloro-4-metoxi-6-oxo-4-heptenoato de metila, a partir do ácido levulínico com amidinas [NH_2CONH_2, $NH_2CR(NH)$ (R = H, Me, Ph, NH_2, SMe e 1*H*-pirazol-1-il), 5-amino-3-metil-1*H*-pirazol e 2-aminotiazol] para obtenção de 3-(6-trifluormetilpirimidina-4-il) propanoatos de metila com estrutura análoga a mediadores glutamatérgicos é relatada. A síntese de 3-(6-trifluormetilpirimidina-4-il)propanohidrazidas também é relatada. A versatilidade desse método foi demostrada através da síntese de quatorze 3(pirimidinil)propanoatos inéditos em rendimentos razoáveis a bons (38-92%). As estruturas moleculares dos produtos foram atribuídas com base nos dados de ressonância magnética nuclear (NMR) de ^1H e ^{13}C e cromatografia de gases acoplada à espectrometria de massas (GC-MS).

The cyclocondensation of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-4-heptenoate and methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate, derived from levulinic acid with amidines [NH_2CONH_2, $NH_2CR(NH)$ (R = H, Me, Ph, NH_2, SMe and 1*H*-pyrazol-1-yl), 5-amino-3-methyl-1*H*-pyrazol and 2-aminothiazole] into pyrimidine and pyrimidine-like derivatives as a new type of glutamate-like 3-(trihalomethylatedpyrimidinyl)propanoate is reported. Preparation of 3-(trihalomethylatedpyrimidinyl) propanohydrazides is also described. The synthetic potential of this straightforward protocol was established by the synthesis of fourteen new 3-(pyrimidinyl) propanoates in regular to good yields (38-92%). The structural assignments were based on the analysis of their ^1H and ^{13}C nuclear magnetic resonance (NMR) and gas chromatography-mass spectrometry (GC-MS) data.

Keywords: pyrimidines, 3-heteroarylpropanoates, levulinic acid, cyclocondensation

Introduction

Research efforts to identify attractive chemical transformations for the conversion of biomass into alternative fuels and useful bulk chemicals have considerably intensified in the last decade. A well-known example is the hydrolysis of lignocellulosic biomass, which is typically catalyzed by enzymes or by mineral acids to give glucose as the intermediate product. Glucose can be converted into bioethanol as an alternative fuel or into various other bulk chemicals. An attractive option is the conversion of glucose into levulinic acid (4-oxopentanoic acid; LA) by acid treatment.[1-3] LA is a versatile building block for the synthesis of various organic compounds.[4-6] Several researchers have described its properties and the potential industrial applications of its derivatives.[7-11] On the other hand, heteroarylpropanoates have been demonstrated to exhibit diverse biological activities, in particular in the central nervous system. Their importance is exemplified by their role as agonist/antagonist mediators of neuronal signals. (*S*)-α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is a classic AMPA receptor agonist, and a large number of heterocyclic Glu analogues are potent and selective agonists at AMPA receptors.[12] The 3-heteroaryl-propanoates are important targets for the development of potent and selective AMPA antagonists and represent

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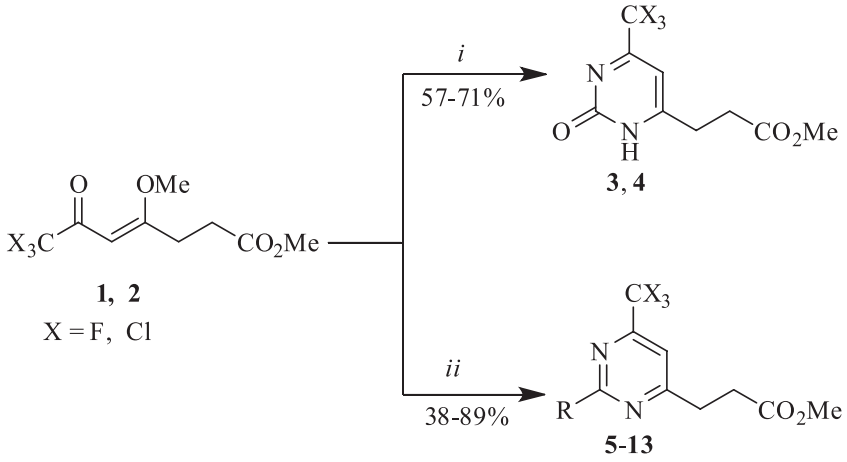
potential drugs for cerebral ischemia or epilepsy. In particular, ethyl 3-(2-ethoxycarbonyl-1*H*-imidazol-4-yl) propenoate and its saturated derivative at micromolar concentrations have been shown to be effective, and phenyl-substituted semicarbazones from LA have been shown to have very good anticonvulsant activity with low neurotoxicity.[13] The synthesis of new drugs targeting glutamatergic or GABAergic systems is also important for the treatment of mood disorders.[14]

Our ongoing interest in functionalized 1,3-dielectrophilic compounds led us to study a new aspect of the application of the acetal acylation method for producing methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates **1** and **2**, which were obtained by trihaloacylation of methyl 4,4-dimethoxypentanoate derived from LA. Our results demonstrated that trihalomethyl-4-alkoxy-3-alken-2-one moieties are regiospecific synthons for several heterocycle classes. With this in mind, our group designed and synthesized a series of methyl 3-(pyrimidinyl)propanoates from the precursors **1** and **2**.

Results and Discussion

Methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates (**1**, **2**) were synthesized in a previous publication.[15] The condensation of 7,7,7-trifluoro-4-methoxy-6-oxo-4-heptenoate (**1**) with urea was investigated. Initially, the cyclocondensation was carried out in isopropanol at 50 °C with $BF_3.OEt_2$ to give a low 20% yield of methyl 3-(2-oxo-6-trifluoromethyl-2,3-dihydropyrimidin-4-yl)propanoate (**3**). Changing the solvent (MeOH) and reaction temperature (25 °C or reflux), the yield did not increase. Therefore, it was used concentrated HCl as an acid catalyst in methanol to obtain product **3** at a better yield of 57% (Scheme 1).[16] The cyclocondensation of methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate was carried out via HCl catalysis in MeOH to give a good 71% yield of methyl 3-(2-oxo-6-trichloromethyl-2,3-dihydropyrimidin-4-yl) propanoate (**4**), after isolation and purification as described in the Experimental section.

For cyclocondensations between precursors **1** and **2** with amidine salts (hydrochloride or sulfate), the process was started based on a previous report on cyclocondensation [3 + 3] of β-alkoxyvinyltrihalomethylketones and amidines under basic NaOH or alkoxy (methoxy, ethoxy) catalysis.[17] Initially, the cyclocondensation between **1** and 2-methyl-2-thiopseudourea sulfate was carried out in methanol with 1 mol L^{-1} NaOH aqueous solution catalysis, a reaction temperature ranging from 25 to 50 °C, and a reaction time of 1-24 h. The results demonstrated that the best relationship between reaction temperature/time and yields was achieved keeping the stirred reactional solution at 25 °C for 1 h, leading to a good 66% yield for pure methyl 3-(2-thiomethyl-6-trifluoropyrimidin-4-yl)propanoate (**8**) (Scheme 1). These conditions were extended to cyclocondensations between the precursor **1** and benzamidine hydrochloride and 1*H*-pyrazol-1-carboxamidine hydrochloride, leading to methyl 3-(2-phenyl-6-trifluoromethylpyrimidin-4-yl)



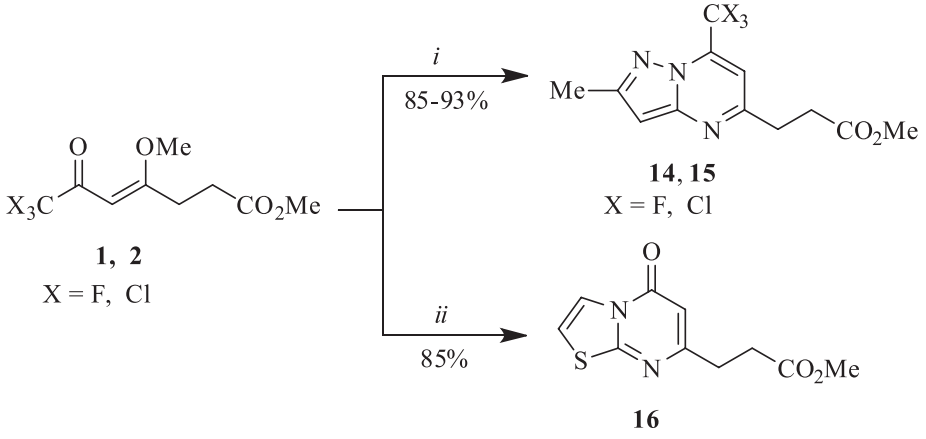
	5	6	7	8	9	10	11	12	13
R	H	Me	Ph	SMe	NH_2	1*H*-pyrazol-1-yl	Ph	SMe	1*H*-pyrazol-1-yl
X	F	F	F	F	F	F	Cl	Cl	Cl

Scheme 1. Conditions for [3+3] cyclocondensation: (i) NH_2CONH_2, MeOH, reflux, 20 h; (ii) $NH_2C(R)=NH$, MeOH:NaOH 1 M (1:1), 25 °C, 4 h.

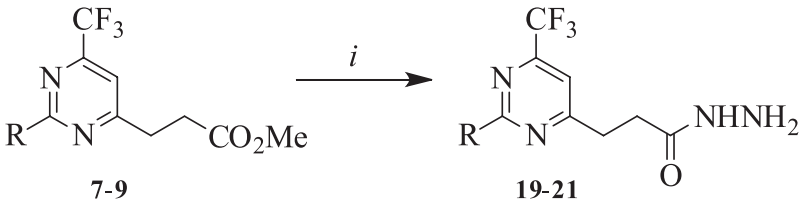
propanoate (**7**) and methyl 3-[2-(1*H*-pyrazol-1-yl)-6-trifluoromethylpyrimidin-4-yl]propanoate (**10**) at good yields of 62 and 73%, respectively (Scheme 1). The cyclocondensation between **1** and acetamidine hydrochloride and guanidine hydrochloride was completed after only 1 h at 50 °C. Varying the reaction time from 1 to 24 h at 25 °C always led to mixtures of product and unconsumed reagents. The products methyl 3-(2-methyl-6-trifluoromethylpyrimidin-4-yl)propanoate (**2**) and methyl 3-(amino-6-trifluoromethylpyrimidin-4-yl) propanoate (**9**) were obtained at reasonable to good yields of 47 and 52%, respectively (Scheme 1). Methyl 3-(6-trifluoromethylpyrimidin-4-yl)propanoate (**5**) was obtained at an acceptable 38% yield after only carrying out the cyclocondensation between **1** and formamidine hydrochloride at 50 °C for 16 h (Scheme 1). Less reaction time led to a mixture of product **5** and unconsumed reagents, and a longer 24 h reaction led to a mixture of product **5** and resinous unidentified oil.

After preparing a fluorinated series of methyl 3-(6-trifluoromethylpyrimidin-4-yl)propanoate derivatives, cyclocondensation reactions were performed between chlorinated precursor **2** and the same series of amidines. The reactions of **2** with 2-methyl-2-thiopseudourea sulfate, benzamidine hydrochloride and 1*H*-pyrazol-1-carboxamidine were carried out at the same conditions used for fluorinated precursor **1**, leading to methyl 3-(2-thiomethyl-6-trichloromethylpyrimidin-4-yl)propanoate (**12**), methyl 3-(2-phenyl-6-trichloromethyl pyrimidin-4-yl) propanoate (**11**) and methyl 3-[2-(1*H*-pyrazol-1-yl)-6-trichloromethyl pyrimidin-4-yl)propanoate (**13**) at very good yields of 67, 72 and 83%, respectively (Scheme 1).

Exploring the synthetic usefulness of **1** and **2**, and expanding the sampling diversity from LA, it was conducted condensations of precursors **1** and **2** with 3-amino-5-methyl-1*H*-pyrazol and 2-aminothiazole. As described in a previous report, the reactions between **1** and **2** and 3-amino-5-methyl-1*H*-pyrazol were carried out in reflux MeCN for 3 h, leading to methyl 3-(2-methyl-7-trihalomethylpyrazolo[1,5-*a*] pyrimidin-5-yl)propanoates **14** and **15** at very good yields of 85 and 93%, respectively.[18] A reaction of 2-aminothiazole carried out in reflux EtOH for 8 h with precursor **1** gave the methyl 7,7,7-trifluoro-4-(2-aminothiazolyl)-6-oxo-4-heptenoate. A reaction of 2-aminothiazole with **2** under the same conditions used to fluorinate precursor **1** led to the cyclic product methyl 3-(5*H*-thiazolo[3,2-*a*]pyrimidin-5-one-7-yl)propanoate (**18**), obtained via cyclization with the elimination of the haloform group.[19]



Scheme 2. Conditions for [3+3] cyclocondensation: (i) 3-amino-5-methyl-1H-pyrazol, AcOH, 118 °C, 16 h; (ii) 2-aminothiazole, EtOH, 78 °C, 2 h.



	7, 19	8, 20	9, 21
R	Ph	SMe	NH_2

Scheme 3. Conditions for hydrazide synthesis: (i) NH2NH2.H2O, EtOH, 78 °C, 2 h.

To explore the reactivity of the methyl 3-(pyrimidinyl) propanoates **7**-**9** series and to obtain the respective hydrazide derivatives, it was conducted reactions with hydrazine monohydrate in ethanol, leading to products **19**-**21** at good 74-92% yields. These hydrazides are important intermediates for the production of biheterocyclic systems with C3 propanoyl spacers.

The structures of methyl 3-(pyrimidinyl)propanoate derivatives **3**-**18** were supported by elemental analysis, gas chromatography-mass spectrometry (GC-MS) and ^{1}H and ^{13}C nuclear magnetic resonance (NMR). Their mass spectra displayed a molecular ion and fragmentation pattern with a base peak [$M^+ - 59$] (see Supplementary Information). The ^{1}H NMR spectra for fluorinated and chlorinated derivatives showed the same feature, displaying a signal related to H-5 from the pyrimidine ring at about δ 6.2 to 7.8 ppm. The signal related to propanoate methylenes consisted of two triplets at δ 2.50 and 3.20 ppm in both series, and the signal from methoxy ester was at δ 3.5 to 3.8 ppm. The ^{13}C NMR spectra showed the characteristic signals for each derivative series. For fluorinated derivatives, a quartet related to the CF_3 group was displayed at about δ 120 ppm with $^{3}J_{CF}$ 275 Hz, the quartet signal related to C6 from the pyrimidine ring was at about δ 155 ppm with J_{CF} 36 Hz, and the narrow quartet related to C5 from the pyrimidine ring was at about δ 133 ppm with $^{4}J_{CF}$ 2.7 Hz. The spectra from chlorinated derivatives showed a characteristic low-intensity signal related to the CCl_3 group at δ 95 ppm. For derivative **18**, there was not any signal related to the CCl_3 group, and a signal related to the carbonyl C5 of the thiazolopyrimidine ring was displayed at δ 158 ppm.

Conclusion

In conclusion, cyclocondensation [3 + 3] between methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates and amidines is an efficient method for synthesizing diverse methyl 3-(pyrimidinyl)propanoate derivatives at good yields. These compounds are interesting structural analogues to central nervous system chemical mediators, making them good subjects for studies of biological activity. Moreover, they are precursors to hydrazide intermediates of biheterocycle systems. To the best of our knowledge, no methyl 3-(pyrimidinyl)propanoates and 3-(pyrimidinyl)propanehydrazides have previously been described.

Experimental

^{1}H and ^{13}C NMR spectra were collected at 300 K using a Bruker 5 mm dual probe on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz, ^{13}C at 100.62 MHz). Chemical shifts (δ) are quoted in ppm from TMS (tetramethylsilane) and coupling constants (J) are given in Hz. Melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus. Mass spectra were registered in an HP 5973 MSD connected to an HP 6890 GC and interfaced by a Pentium PC. GC was equipped with a split-splitless injector, cross-linked to an HP-5 capillary column (30 m, 0.32 mm i.d.), and helium was used as the carrier gas. CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (Universidade de São Paulo (USP), Brazil).

Supplementary Information

Spectral data and spectra of synthesized compounds are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgements

The authors are grateful for the financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Universal grant 657781847796276 4-01), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS, grant PqG 1016236). The fellowships from CNPq (A. A. Souto and J. L. Malavolta) are also acknowledged.

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Submitted: October 2, 2012
Published online: March 22, 2013