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Tetrahedron Letters 49 (2008) 2789–2791
Tetrahedron Letters

A facile and regioselective synthesis of rimonabant through an enamine-directed 1,3-dipolar cycloaddition

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Received 18 January 2008; revised 22 February 2008; accepted 22 February 2008
Available online 29 February 2008

Abstract

Rimonabant is a high-potency cannabinoid type-1 (CB_1) receptor inverse agonist that has recently been approved in the European Union as a treatment for obesity. Current methods of synthesis require several steps that have long reaction times and/or lack regioselectivity. Here we present a novel, regioselective synthesis of rimonabant though an enamine-directed 1,3-dipolar cycloaddition. In addition, we present a new and more reactive hydrazonoyl halide for the generation of the requisite nitrile imine dipole.

Keywords: CB_1 Receptor; 1,5-Diarylpyrazole; Rimonabant; 1,3-Dipolar cycloaddition

1. Introduction

Cannabinoid type-1 (CB_1) receptors are promising targets for the therapeutic treatment of several neurobiological disorders. Rimonabant (Acomplia® or Zimulti®, **1**),[1] a selective CB_1 receptor inverse agonist, has recently been approved in the European Union (EU) for the treatment of obesity. Its therapeutic potential may extend to the treatment of addiction[2] and neurodegenerative diseases.[3] At present there are only a few published routes for its synthesis.[4–7] The 1,5-diarylpyrazole core of **1** has been the subject of extensive structure–activity relationship studies to define more strictly the key structural requirements for an improved pharmacological profile within this structural class.[8]

The usual method for the synthesis of **1** and its cognates employs a base-catalyzed reaction of the enolate of a substituted-propiophenone with diethyl oxalate for 16 h (Scheme 1). The resulting diketone ester lithium enolate (**2**) is immediately treated with a substituted-phenylhydrazine hydrochloride in ethanol for 20 h. The crude mixture of product hydrazones (**3** and **4**) are isolated by filtration, dried under vacuum and then heated at reflux in acetic acid for 24 h, yielding a mixture of regioisomeric pyrazoles (**5** and **6**).[5] After column purification, **6** is hydrolyzed to the corresponding carboxylic acid (**7**) under basic conditions. In final steps, **1** or one of its cognates is formed by conversion of the appropriate acid into the acyl chloride and addition of 1-aminopiperidine. Although this is an effective method for the production of several 1,5-diarylpyrazole CB_1 receptor ligands, it has several limitations. These include several steps with long reaction times, structural modification limited by the few commercially available substituted-phenylhydrazines and lack of regioselectivity.

It has long been known that 1,5-diarylpyrazoles can be rapidly and regioselectively synthesized through a 1,3-dipolar cycloaddition reaction, with the appropriate dipolarophile and nitrile imine dipole (Scheme 2).[9,10] However, we have not found a reported route for **1** or its cognates through this synthetic pathway. Here we fill-in this gap by describing a regioselective synthesis of **1**, that can be extended to its cognates, through an enamine-directed

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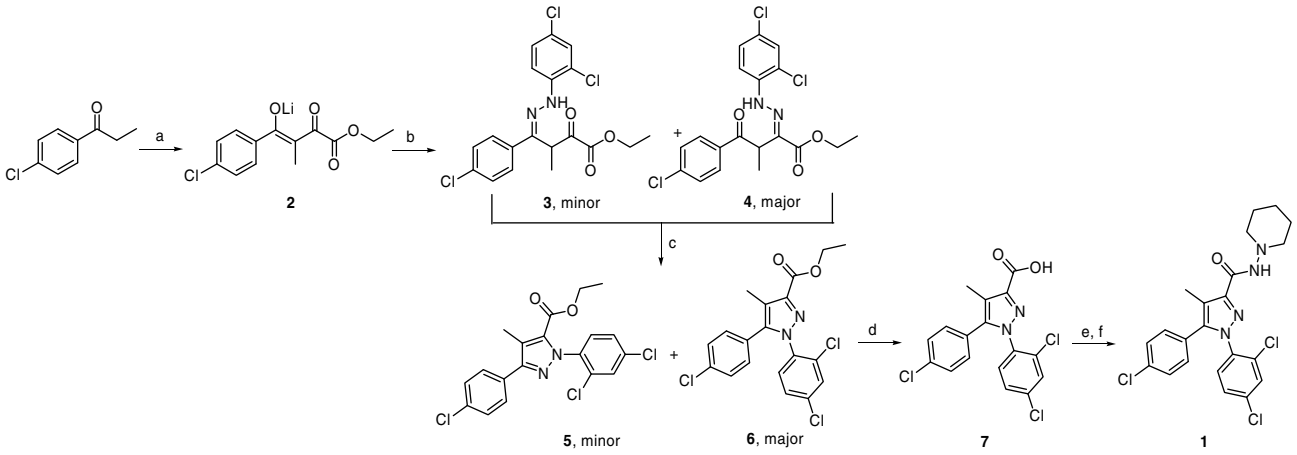
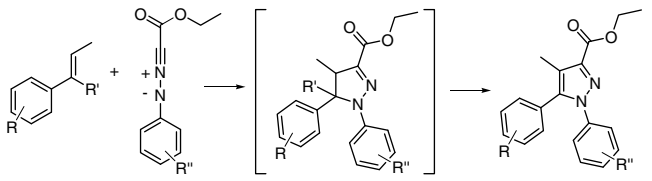
doi:10.1016/j.tetlet.2008.02.132



Scheme 1. Synthesis of **1**. Reagents and conditions: (a) LiHMDS, Et_2O, diethyl oxalate, −78 °C; (b) 2,4-dichlorophenylhydrazine HCl, EtOH; (c) AcOH, Δ; (d) KOH, MeOH; (e) $SOCl_2$, toluene; (f) 1-aminopiperidine, TEA, DCM.



Scheme 2. Synthesis of 1,5-diarylpyrazole from a 1,3-dipolar cycloaddition reaction.

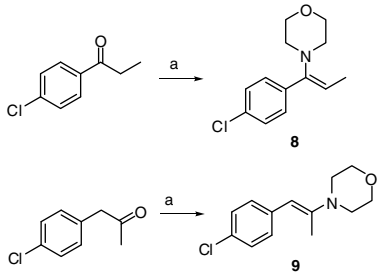
1,3-dipole cycloaddition. Moreover, during the course of this investigation we have identified a new and more reactive hydrazonoyl halide for the generation of the requisite nitrile imine dipole.

2. Results and discussion

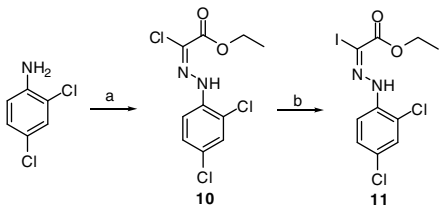
The generation of a morpholine enamine from 4′-chloropropiophenone was a logical starting point for the formation of the requisite 1,1-disubstituted-propene enamine dipolarophile (**8**, Scheme 3). This is because its electron pairing with a corresponding nitrile imine would regioselectively form the 1,5-diarylpyrazole core of **1**. There are several known routes to the synthesis of enamines. The most attractive route for our purpose was a modification of the procedure introduced by White and Weingarten.[11,12] Although this method requires near stoichoimetric amounts of air and moisture-sensitive $TiCl_4$, it is known to generate enamines rapidly to near completion for a range of ketones and aldehydes. Equally important, the following work-up is simple and allows the crude enamine to be used in the next step without further purification. Hence, this was the method of choice for the synthesis of **1** (Scheme 2). Also, the morpholine enamine derived from 4-chlorophenylacetone yielding a 1,2-disubstituted-propene dipolarophile (**9**, Scheme 3) was prepared in order to provide additional evidence for the regioselective outcome of our new route.

Chloro[(2,4-dichlorophenyl)hydrazono]ethyl acetate (**10**)[13] is a well-known precursor for the base-catalyzed in situ generation of a nitrile imine. Furthermore, the resulting nitrile imine would combine with morpholine enamine (**8**) to give the 1,5-diarylpyrazole base core of **1**. The hydrazonoyl chloride (**10**) was synthesized by treating ethyl 2-chloro-acetoacetate with the diazonium salt of 2,4-dichloroaniline giving an air-stable and easy to handle solid (Scheme 4). However, this hydrazonoyl chloride has low reactivity for in situ generation of the nitrile imine. In order to increase reactivity of the hydrazonoyl chloride, we used the Finkelstein reaction to exchange the chlorine atom with an iodine atom to give **11**.

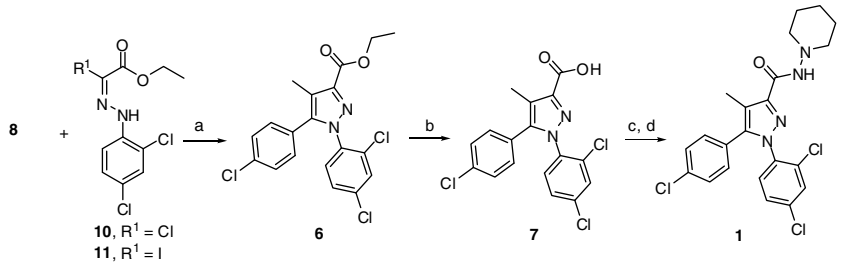
Indeed, in our experiments the reaction of **8** with **10** in the presence of triethylamine (3 equiv) required raised



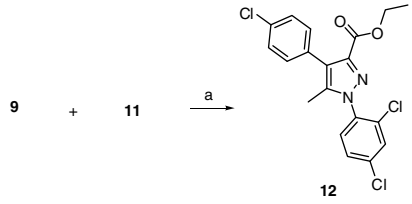
Scheme 3. Synthesis of enamines **8** and **9**. Reagents and conditions: (a) morpholine, DIPEA, $TiCl_4$, toluene. Yields: 83% for **8** and 87% for **9**.



Scheme 4. Synthesis of hydrazonoyl halides **10** and **11**. Reagents, conditions and yields: (a) HCl, $NaNO_2$, AcONa, ethyl 2-chloro-acetoacetate; (b) NaI, acetone: Yield: 92% for **11**.



Scheme 5. Synthesis of **1** through a 1,3-dipolar cycloaddition reaction. Reagents, conditions and yields: (a) TEA (3 equiv), DME, rt, 22%; (b) LiOH, THF, H_2O; (c) $(COCl)_2$, DMF(cat), DCM, (d) 1-aminopiperidine, TEA, DCM, 67%.



Scheme 6. Synthesis of **12** through a 1,3-dipolar cycloaddition reaction. Reagents, conditions and yield: (a) toluene, TEA (3 equiv), Δ, 11%.

temperatures (>60 °C) and gave significant discoloration of the reaction solution. In contrast, the reaction of **8** with **11** in the presence of triethylamine (3 equiv) proceeded at room temperature to give yields similar to that with **10** at raised temperature (22 vs 19%) (Scheme 5). At the same time there was very little discoloration of the reaction solution. In order to complete our synthesis of **1**, the ethyl ester of **6** was hydrolyzed to **7** under basic conditions. Then **7** was converted into the acyl chloride, to which was added 1-aminopiperidine.

To provide additional evidence for the regioselective outcome, the 1,2-disubstituted-propene enamine (**9**) was treated with **11** in the presence of triethylamine (3 equiv) (Scheme 6). This gave slightly lower yields of ring product (11%) and also required higher temperature (90 °C).

In conclusion, we have developed a novel regioselective approach to **1** through an enamine-directed 1,3-dipole cycloaddition reaction. The regioselective outcome was verified through the synthesis of the 1,4-diarylpyrazole (**12**). In addition, we have developed a new, more reactive hydrazonoyl halide precursor (**11**) for the in situ generation of a nitrile imine.

Acknowledgments

This work was supported by the Intramural Program of the National Institutes of Health (NIMH) (Project # Z01-MH-002795). Mr. S. R. Donohue was also supported with a studentship under the NIH-Karolinska Institutet Graduate Training Partnership in Neuroscience.

Supplementary data

Experimental details and molecular characterization (i.e., Mp, ^{1}H NMR, ^{13}NMR, LC–MS, GC–MS, HRMS, and elemental analysis) are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.132.

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