Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4887–4890

One-pot synthesis of functionalized hydantoin derivatives via a four-component reaction between an amine, an arylsulfonyl isocyanate and an alkyl propiolate or dialkyl acetylenedicarboxylate in the presence of triphenylphosphine

Abdolali Alizadeh* and Ehsan Sheikhi

Department of Chemistry, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran

Received 10 March 2007; revised 29 April 2007; accepted 10 May 2007
Available online 17 May 2007

Abstract—An effective route to functionalized hydantoin derivatives is described, involving the reaction of a urea derivative resulting from the addition of a primary amine to an arylsulfonyl isocyanate, and an alkyl propiolate or dialkyl acetylenedicarboxylate in the presence of triphenylphosphine. The reactive 1:1 intermediate obtained from the addition of triphenylphosphine to the alkyl propiolate or dialkyl acetylenedicarboxylate was trapped by NH-acids such as the urea derivative to produce functionalized hydantoin derivatives.

Hydantoins (imidazolidine-2,4-diones) are an important class of heterocycles, since many hydantoin-containing natural and synthetic products exhibit diverse biological activities, such as antitumor,[1] antiarrhythmic,[2] anticonvulsant,[3] herbicidal,[4] and others.[5–7]

Phenytoin (5,5-diphenylhydantoin) is one of the most widely used anticonvulsants. The site of the action of phenytoin is the neuronal voltage-sensitive sodium channel.[8] However, no exact information about the location and nature of this site has been collected so far.

The relationship between molecular structure and activity has been thoroughly studied for phenytoin and its derivatives.[8–10] A general model compound with anticonvulsant activity,[9] comprises two aromatic rings or their equivalents in a suitable orientation and a third, heterocyclic region, usually a cyclic ureide. Evaluation of binding to the neuronal voltage-dependent sodium channel together with conformational studies for hydantoin and diphenylhydantoin derivatives revealed their optimum molecular conformation. According to these studies, one of the phenyl rings should be almost coplanar with the hydantoin moiety.[8] The activity of the derivatives of hydantoin at serotonin receptors (5-HT1D and 5-HT2A) was studied by Glen et al.,[11] who postulated a pharmacophore composed of a protonated amine site, an aromatic site, a hydrophobic pocket and two hydrogen-bonding sites. As suggested by Kolasa et al.,[12] benzylidene derivatives of hydantoin, which have a methylene 'bridge' (to the phenyl ring) at the 5-position, are weak anticonvulsants.

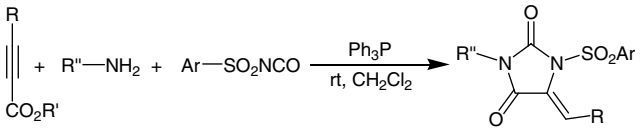
Herein, we report a simple one-pot reaction between a urea derivative, derived from the addition of a primary amine to an arylsulfonyl isocyanate, and an alkyl propiolate or dialkyl acetylenedicarboxylate in the presence of triphenylphosphine leading to hydantoin derivatives[13] **4** (Scheme 1). The reaction proceeded via a smooth 1:1:1 addition in dichloromethane at ambient temperature, to produce hydantoin derivatives **4a**–**e** in 80–90% yields (Scheme 1).

The structures of compounds **4a**–**e** were deduced from their elemental analysis, IR, and ^{1}H and ^{13}C NMR spectra.

The mass spectrum of **4a** displayed a molecular ion peak at m/z 400, which was consistent with the 1:1:1 adduct of

Keywords: Alkyl propiolate; Amine; Arylsulfonyl isocyanate; Dialkyl acetylenedicarboxylate; Hydantoin; Triphenylphosphine; Multicomponent reaction.
* Corresponding author. Tel.: +92 21 88006631; fax: +98 21 88006544; e-mail: aalizadeh@modares.ac.ir

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.061



1 2 3 4

4	R	R"	Ar	%Yield of 4
a	CO_2Me	$PhCH_2$-	Ph	80
b	CO_2Me	$PhCH_2$-	*p*-$CH_3C_6H_4$-	80
c	CO_2Me	*o*-$ClC_6H_4CH_2$-	*p*-$CH_3C_6H_4$-	85
d	H	*o*-$ClC_6H_4CH_2$-	*p*-$CH_3C_6H_4$-	90
e	H	2-Ethylhexyl	*p*-$CH_3C_6H_4$-	80

Scheme 1.

benzylamine, benzenesulfonyl isocyanate and dimethyl acetylenedicarboxylate. The ^1H NMR spectrum of **4a** exhibited three single sharp lines arising from methoxy ($\delta = 3.58$ ppm) and methylene ($\delta = 5.30$ ppm) protons along with a vinylic CH ($\delta = 5.88$ ppm). The phenyl moieties gave rise to characteristic signals in the aromatic region of the spectrum. The ^1H decoupled ^{13}C NMR spectrum of **4a** showed 14 distinct resonances in agreement with the structure of methyl 2-[1-benzyl-2,5-dioxo-3-(phenylsulfonyl)tetrahydro-4*H*-imidazol-4-yilidene]acetate.

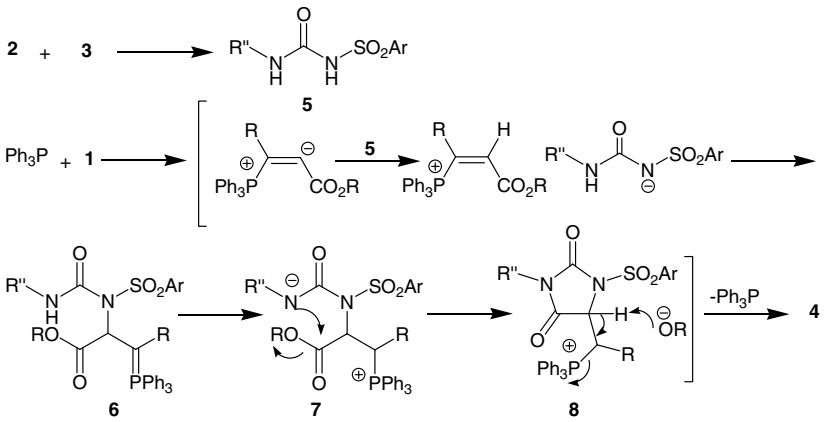
The ^1H and ^{13}C NMR spectra of compounds **4b–e** were similar to those of **4a**, except for the aromatic moiety, which exhibited characteristic signals with appropriate chemical shifts for the specific substitution patterns.[13]

Although the mechanism of the reaction between triphenylphosphine and alkyl propiolates or dialkyl acetylenedicarboxylates **1** in the presence of urea derivative **5** (derived from addition of primary amine **2** to arylsulfonyl isocyanate **3**) has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2. Based on the well-established chemistry of trivalent phosphorus nucleophiles,[14–21] it is reasonable to assume that product **4** results from initial addition of triphenylphosphine to the alkyl propiolate or dialkyl acetylenedicarboxylate and subsequent protonation of the 1:1 adduct by the urea derivative **5** acting as an NH-acid. Next, the positively charged ion might be attacked by the conjugate base of the NH-acid to form phosphorane **6**, which in turn is converted to betaine **7**. Cyclization of betaine **7** and subsequent loss of triphenylphosphine leads to compound **4** (Scheme 2).

In conclusion, we have developed a convenient, one-pot method for preparing stabilized hydantoins. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substrates can be reacted without any prior activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

References and notes

1. Struck, R. F.; Kirk, M. C.; Rice, L. S.; Suling, W. J. *J. Med. Chem.* **1986**, *29*, 1319–1321.
2. Matsukura, M.; Daiku, Y.; Ueda, K.; Tanaka, S.; Igarashi, T.; Minami, N. *Chem. Pharm. Bull.* **1992**, *40*, 1823–1827.
3. Perry, J. K.; Newmark, M. E. *Ann. Int. Med.* **1979**, *89*, 207.
4. (a) Haruyama, H.; Takayama, T.; Kinoshita, T.; Kondo, M.; Nakajima, M.; Haneishi, T. *J. Chem. Soc., Perkin. Trans. 1* **1991**, 1637–1640; (b) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S.; Sato, S. *Tetrahedron* **1991**, *47*, 2111–2120; (c) Mio, S.; Shiraishi, M.; Sugai, S.; Haruyama, H.; Sato, S. *Tetrahedron* **1991**, *47*, 2121–2132; (d) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133–2144; (e) Chemla, P. *Tetrahedron* **1993**, *34*, 7391–7394; (f) Harrington, P. M.; Jung, M. E. *Tetrahedron* **1994**, *35*, 5145–5148; (g) Fischer, H. P.; Buser, H. P.; Chemla, P.; Huxley, P.; Lutz, W.; Mirza, S.; Tombo, G. M. R.; van Lommen, G.; Sipido, V. *Bull. Soc. Chim. Belg.* **1994**, *103*, 565–581; (h) Sano, H.; Sugai, S. *Tetrahedron* **1995**, *51*, 4635–4646.
5. (a) Bichard, C. J. F.; Mitchell, E. P.; Wormald, M. R.; Watson, K. A.; Johnson, L. N.; Zographos, S. E.; Koutra, D. D.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 2145–2148; (b) Brandstetter, T. W.; Kim, Y. H.; Chan Son, J.; Taylor, H. M.; de Q Lilley, P. M.; Watkin, D. J.; Johnson, L. N.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 2149–2152; (c) Brandstetter, T. W.; de la Fuente, C.; Kim, Y. H.;



Scheme 2.