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A facile protocol for the preparation of 5-alkylidene and 5-imino substituted hydantoins from *N,N′*-disubstituted parabanic acids

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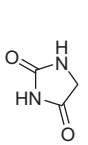
ABSTRACT

A convenient procedure for the preparation of various substituted (thio)hydantoins is described. The method is based on Wittig and aza-Wittig reactions of parabanic acids with phosphonium ylides. The reactions occurred both regio- and stereo-selectively.

Five-membered rings containing two heteroatoms are privileged structures with proven utility in medicinal chemistry.[1] One example of such a heterocycle is hydantoin (**I**), an important pharmacophore.[2] Several hydantoin alkaloids (for example **II**–**IV**) have been extracted from sponges, corals or marine organisms,[2,3] and some synthetic drugs such as phenytoin (**V**) and nilutamide (**VI**) contain a hydantoin skeleton.[1,2,4] Due to the interesting features of hydantoins, recent progress has led to the development of new methods for the preparation of these compounds.

Many processes have been published for the preparation of substituted hydantoins including the Bucherer–Bergs synthesis,[5a] the Eldman method,[5b] the Staudinger reaction,[5c] microwave-assisted approaches,[5d] a domino process,[5e] Ugi reactions[5f,g] and MCRs or solid-phase techniques.[2] Nevertheless, new methods for the rapid synthesis of structurally varied and functionalized hydantoins remain desirable.



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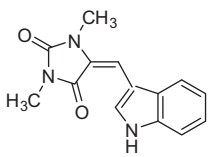
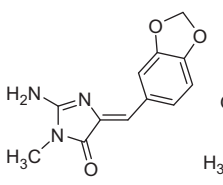
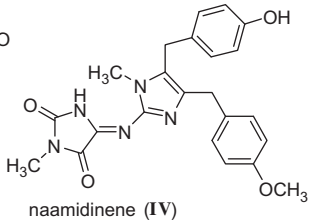


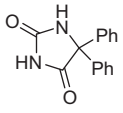
3′-deimino-3′-oxaaplysinopsin (**II**)



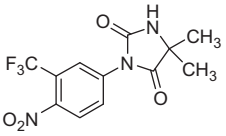
lucettamine B (**III**)



naamidinene (**IV**)



phenytoin (**V**)



nilutamide (**VI**)

Wittig and aza-Wittig reactions are often used for the synthesis of acyclic and cyclic carbonyl compounds. In addition, the ability to perform the reactions in neutral solvents, without catalysts, at mild temperatures is advantageous.[6]

As an efficient new process for the preparation of alkylidene- and imino-substituted hydantoins, the reactions of Wittig reagents with parabanic acid derivatives are described herein by means of a two-step synthetic procedure: a cyclization process involving readily accessible urea and oxalyl chloride producing parabanic

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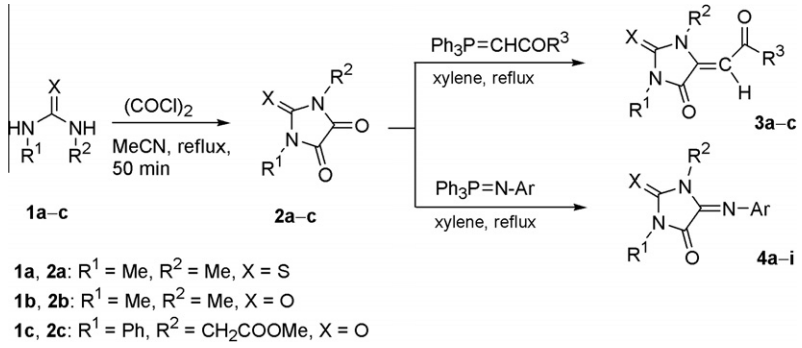


Scheme 1. Preparation of various substituted hydantoins in the two steps starting from ureas.

Table 1
Synthetic hydantoins **3a–c** and **4a–i** prepared using Wittig/aza-Wittig reactions

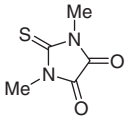
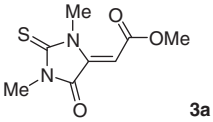
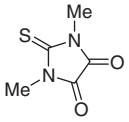
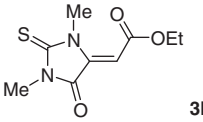
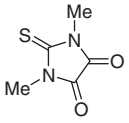
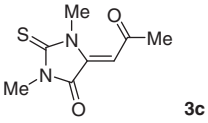
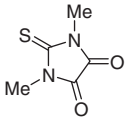
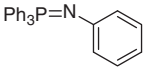
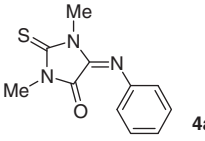
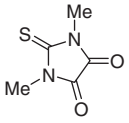
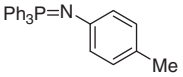
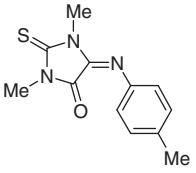
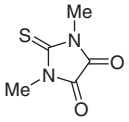
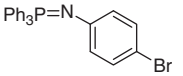
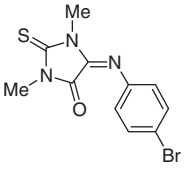
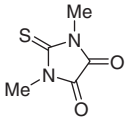
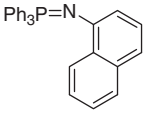
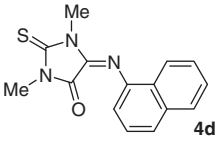
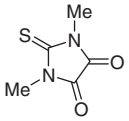
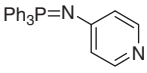
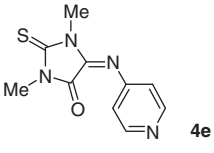
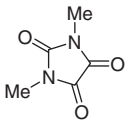
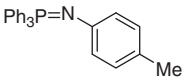
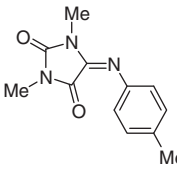
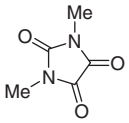
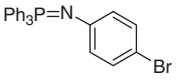
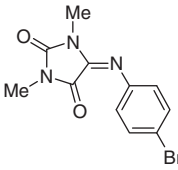
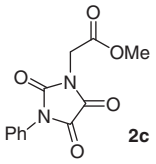
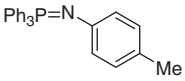
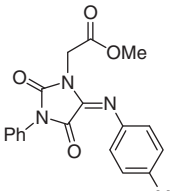
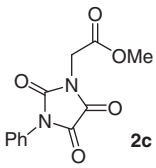
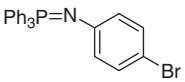
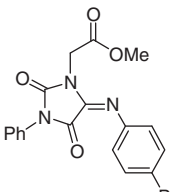
Entry	Substrate	Wittig reagent	Hydantoin (product)	Time (min)	Yield[a] (%)	Mp (°C)
1	 **2a**	$Ph_3P{=}CHCOOMe$	 **3a**	20	77	124
2	 **2a**	$Ph_3P{=}CHCOOEt$	 **3b**	20	81	58
3	 **2a**	$Ph_3P{=}CHCOMe$	 **3c**	20	83	73
4	 **2a**		 **4a**	20	79	96
5	 **2a**		 **4b**	20	81	97
6	 **2a**		 **4c**	20	73	148
7	 **2a**		 **4d**	20	78	189
8	 **2a**		 **4e**	20	65	100

Table 1 (*Continued*)

Entry	Substrate	Wittig reagent	Hydantoin (product)	Time (min)	Yield[a] (%)	Mp (°C)
9	 **2b**		 **4f**	60	75	Oil[b]
10	 **2b**		 **4g**	60	70	100
11	 **2c**		 **4h**	120	61	142
12	 **2c**		 **4i**	120	56	159

[a] Isolated yield.
[b] Lit[10] yellow oil.

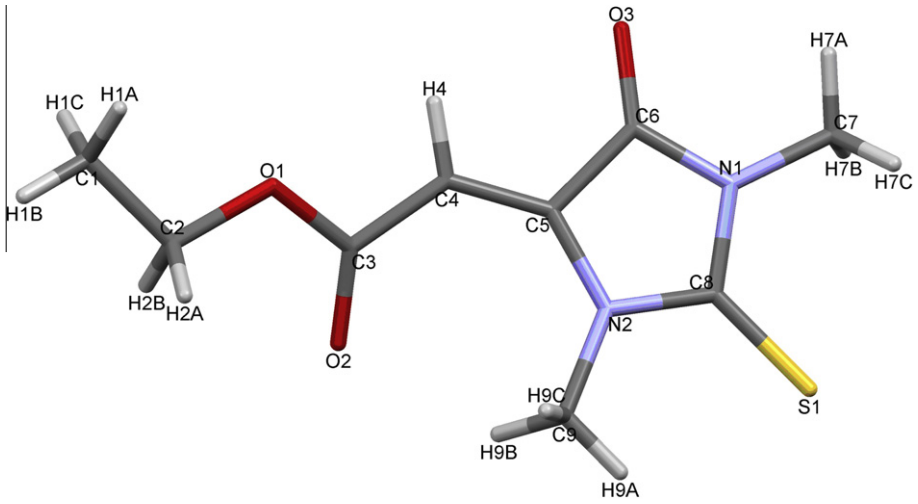


Figure 1. X-ray crystal structure of **3b**.

acids, followed by regio- and stereo-selective Wittig reaction with the parabanic acids.

Parabanic acid derivatives **2a–c** (Scheme 1) have been previously synthesized using various procedures.[7] In this study, compounds **2a–c** were prepared via cyclizations of ureas **1a–c** with oxalyl chloride.[8]

The parabanic acids **2a–c** reacted regioselectively with aryliminophosphoranes and acylmethylenephosphoranes in xylene at reflux to afford 5-imino **4a–i** or 5-methylidene **3a–c** substituted hydantoins (Scheme 1).[9] While reactions run in xylene resulted in moderate to good yields (56–83%) within 2 h, the use of toluene resulted in very long reaction times and poor yields. In addition,

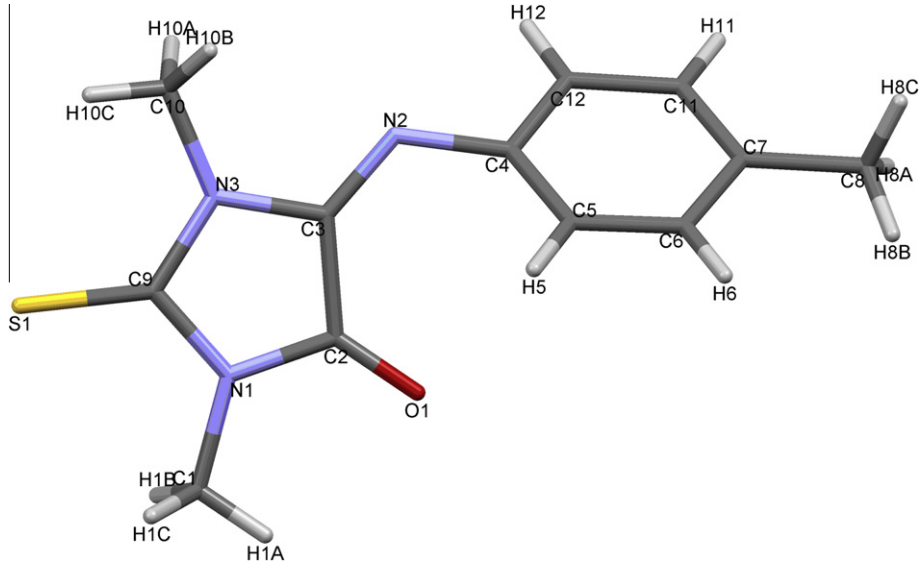


Fig. 2. X-ray crystal structure of **4b**.

the Wittig reagents reacted much faster with 2-thioxo substituted imidazolidines than with 2-oxo substituted imidazolidines in xylene (Table 1). All the products **3a**–**c** and **4a**–**i** were purified by column chromatography.

The Wittig reagents attacked the amide carbonyl of the parabanic acids, but not the urea carbonyl. In addition, with parabanic acid derivative **2c**, which contained different substituents attached to the nitrogen atoms, the Wittig reagents reacted regioselectively on the alkyl-N–C=O group.

The ^{1}H NMR spectrum of **3a** showed a methine proton at δ 5.98, methoxy protons at δ 3.80 and methyl protons at δ 3.84 and δ 3.36. The ^{13}C NMR spectrum exhibited one thione and two carbonyl carbons at δ 181.5 (urea), δ 164.4 and δ 163.6 (ester and amide), C=CH carbons at δ 135.9 and δ 99.4 and a methoxy and two methyl carbons at δ 52.2, δ 34.6 and δ 29.0. In the ^{1}H NMR spectra, the signals of the methine protons of products **3a**–**c** resonated between 6 and 7 ppm. These observations were consistent with the (*Z*)-geometry for the reaction products.

Unambiguous evidence for the structures of both 5-alkylidene and 5-imino substituted hydantoins was obtained by X-ray analyses of crystals of **3b** and **4b** (Figs. 1 and 2).[11]

In conclusion, we have described a simple, rapid and catalyst-free procedure for the synthesis of variously substituted hydantoin and thiohydantoin derivatives from parabanic acids by regioselective Wittig reactions.

Acknowledgements

The authors are grateful to The Medicinal Plants and Medicine Research Centre of Anadolu University for the use of the X-ray diffractometer.

Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR spectral data of all synthesized compounds are reported along with crystallographic data for compounds **3b** and **4b**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.129.

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8. *Representative procedure for the preparation of parabanic acid derivatives by the reaction between ureas **1** and oxalyl chloride*: To a CH_3CN solution of **1a** (1.04 g, 10 mmol) was added oxalyl chloride (1.26 g, 10 mmol), and the mixture was stirred at reflux for 50 min. The solvent was removed on a rotary evaporator and the residue was recrystallized from cyclohexane to give compound **2a**. Orange crystals, yield 1.45 g, 92%; mp: 98–100 °C. FT–IR (ATR): 1763 (C=O), 1331 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.42 (s, 6H, 2 × Me); ^{13}C NMR (100 MHz, $CDCl_3$): 181.5 (C=S), 155.3 (2 × C=O), 28.2 (2 × Me). Anal. Calcd for $C_5H_6N_2O_2S$ (158 g/mol): C, 37.97; H, 3.82; N, 17.71; S, 20.27. Found: C, 38.11; H, 3.85; N, 17.63; S, 20.06%.
9. *Representative procedure for the preparation of hydantoins from the reaction between parabanic acids **2** and a Wittig reagent*: To a boiling xylene solution of **2a** (0.158 g, 1 mmol) was added (methoxycarbonylmethylene) triphenylphosphorane, and the mixture was stirred under reflux for 20 min. The solvent was removed on a rotary evaporator, and the residue was subjected to column chromatography on silica gel 60 HF_{254}; elution with $CHCl_3$ afforded

the product **3a**. Orange crystals, yield 0.165 g, 77%; FT–IR (ATR): 1744, 1700 (C=O), 1653 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 5.98 (s, 1H, =CH), 3.84 (s, 3H, N(3)Me), 3.80 (s, 3H, OMe), 3.36 (s, 3H, N(2)Me); ^{13}C NMR (100 MHz, $CDCl_3$): 181.5 (C=S), 164.4 (COOMe), 163.6 (N–C=O), 135.9 (C=CH), 99.4 (C=CH), 52.3 (OMe), 34.6, 29.0 (2 × NMe). Anal. Calcd for $C_8H_{10}N_2O_3S$ (214 g/mol): C, 44.85; H, 4.70; N, 13.08; S, 14.97. Found: C, 44.79; H, 4.72; N, 13.16; S, 14.81%.

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11. X-ray crystallographic data for structures **3b** and **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 874366 and 875257, respectively. Copies of these data can be obtained, free of charge, on application to the CCDC (deposit@ccdc.cam.ac.uk).