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Naturally occurring bioactive 5-ethylidenehydantoins as inspiration for the development of analogues

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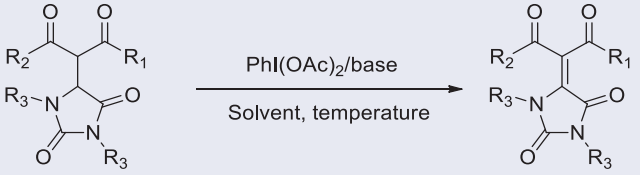
ABSTRACT

Many naturally occurring 5-ethylidenehydantoins and their derivatives exhibit extensive biological activities; this characteristic has inspired us to prepare analogues. Fourteen such analogues with the core structure of 5-ethylidenehydantoin were synthesized from readily available components with yields of up to 82%.

GRAPHICAL ABSTRACT



R_1, R_2 = aryl, alkyl or alkoxyl ; R_3 = *i*-Pr, cyclohexyl

14 examples, 35% to 82% yield

ARTICLE HISTORY
Received 9 September 2017

KEYWORDS
5-ethylidenehydantoins; skeleton; tetrasubstituted

Introduction

5-Ethylidenehydantoins have a unique skeleton, and many naturally occurring 5-ethylidenehydantoins exhibit a variety of biological activities.[1–4] For instance, anticancer, GlyR-modulating, antikinase and naturally toxic effects are produced by the natural compounds phenylmethylenehydantoin (PMH);[5,6] 8*E*-3′-deimino-3′-oxoaplysinopsin and 8*Z*-3′-deimino-3′-oxoaplysinopsin;[7] three pyrrole-imidazole alkaloids [(*E*)-axinohydantoin, (*Z*)-axinohydantoin and (*Z*)-debromoaxinohydantoin];[8,9] and parazoanthines B-E,[10] respectively (Scheme 1). In addition, certain 5-spiro hydantoins, such as 6-((5*S*,9*R*)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro-[4.4]nonan-7-yl) nicotinic acid[11] and 5-[(5*S*,9*R*)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-

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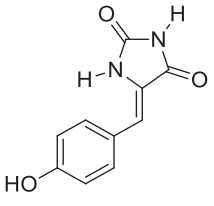
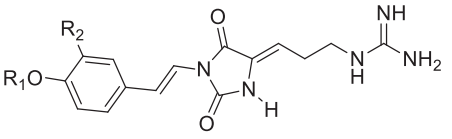
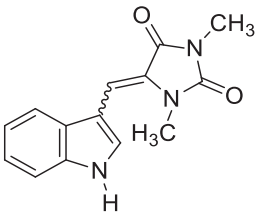


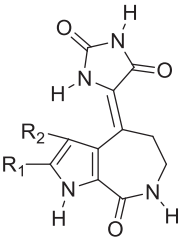
PMH



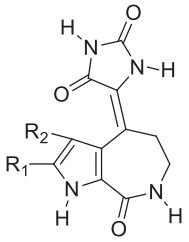
R_1=R_2=H parazoanthine B
R_1=Me, R_2=H parazoanthine C
R_1=Me, R_2=Br parazoanthine E



8*E*-3'-deimino-3'-oxoaplysinopsin
8*Z*-3'-deimino-3'-oxoaplysinopsin



(*Z*)-axinohydantoin R_1=Br, R_2=H
(*Z*)- debromoaxinohydantoin R_1=R_2=H
(*Z*)-bromoaxinohydantoin R_1=R_2=Br



(*E*)-axinohydantoin R_1=Br, R_2=H
(*E*)- debromoaxinohydantoin R_1=R_2=H
(*E*)-bromoaxinohydantoin R_1=R_2=Br

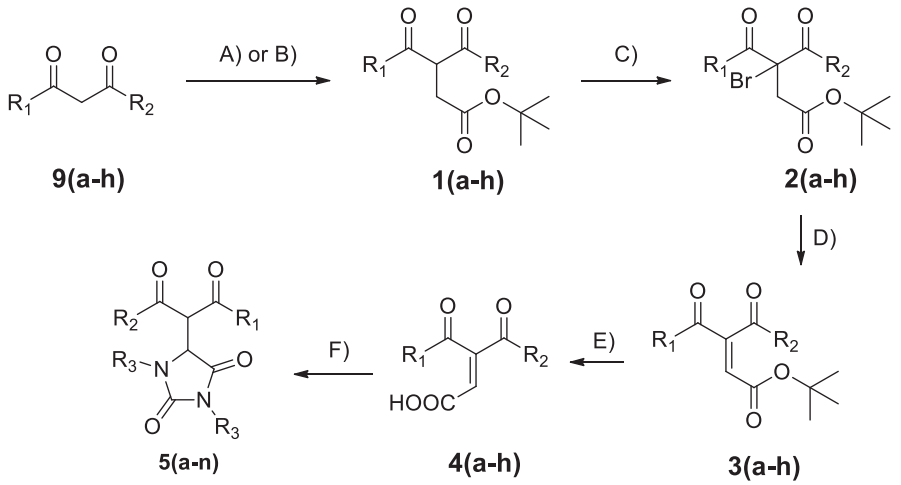
Scheme 1. Naturally occurring 5-ethylidenehydantoins.

dioxo-1,3,7-triazaspiro[4.4]non-7-yl-methyl]-3-thiophenecarboxylic acid, have been selected for testing in clinical trials.[12]

Interestingly, 5-ethylidenehydantoins are also extremely important synthetic intermediates.[13] 5-Ethylidenehydantoins can undergo epoxidation, methanol addition and conjugate addition reactions with different types of nucleophiles to produce numerous hydantoin derivatives that exhibit a variety of biological activities.[14–21] Unsurprisingly, these features have inspired chemists to design synthetic protocols. To date, methods to obtain 1,5-di-, 3,5-di- and 5-substituted ethylidenehydantoins are readily accessible;[22–24] however, there are few strategies for preparing tetrasubstituted 5-ethylidenehydantoins. Given the unique core structure and potent biological activities of 5-ethylidenehydantoins, we report here a representative scenario for synthesizing these compounds from readily available components with the objective of constructing this core structure and providing available analogues for screening biological activities.

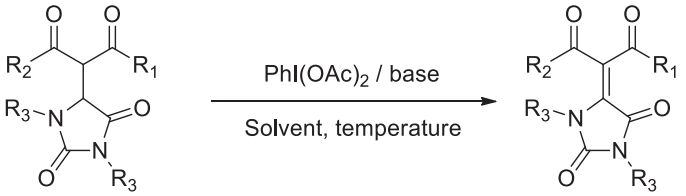
Results and discussion

To achieve our objective, we first synthesized an array of suitably activated α,β-unsaturated carboxylic acids bearing two carbonyl groups at the β position. Alkylation, bromination and dehydrobromination were performed in sequence. The *t*-butyl group was selectively removed using trifluoroacetic acid (Scheme 2). Second, with activated α,β-unsaturated carboxylic acids in hand, we induced these molecules to react effectively with symmetric carbodiimides to afford an array of 1,3,5-trisubstituted hydantoins (with *d* and *r*



Scheme 2. Preparation of suitably activated α,β-unsaturated carboxylic acids and 1,3,5-trisubstituted hydantoins. (A) *t*-butyl bromoacetate, K_2CO_3, CH_3CN;[26] (B) *t*-butyl bromoacetate, NaH, THF;[27] (C) NBS, DBU (15%), CH_2Cl_2;[28] (D) Et_3N, Et_2O;[29] (E) CF_3COOH, CH_2Cl_2;[30] (F) DCC or DIC.[31]

Entry	Substrate	R_1	R_2	R_3	Base	Solvent	Temperature (°C)	Time (min)	Product	Yield (%)
1	**5a**	Ph	Ph	c-C_6H_{11}-	none	CH_3CN	40	30	**6a**	trace
2	**5a**	Ph	Ph	c-C_6H_{11}-	$KHCO_3$	CH_3CN	40	30	**6a**	15
3	**5a**	Ph	Ph	c-C_6H_{11}-	K_3PO_4	CH_3CN	72	5	**6a**	64
4	**5a**	Ph	Ph	c-C_6H_{11}-	K_3PO_4	CH_3CN	72	49	**6a**	68
5	**5a**	Ph	Ph	c-C_6H_{11}-	K_3PO_4	CH_3CN	72	30	**6a**	66
6	**5a**	Ph	Ph	c-C_6H_{11}-	KOH	Toluene	90	16	**6a**	65
7	**5a**	Ph	Ph	c-C_6H_{11}-	K_3PO_4	Toluene	90	30	**6a**	82
8	**5a**	Ph	Ph	c-C_6H_{11}-	DMAP	Toluene	90	30	**6a**	68
9	**5b**	Ph	Ph	*i*-Pr	K_3PO_4	CH_3CN	40	30	**6b**	41
10	**5b**	Ph	Ph	*i*-Pr	K_3PO_4	Toluene	90	30	**6b**	61
11	**5c**	Ph	CH_3	c-C_6H_{11}-	DMAP	Toluene	90	30	**6c**	72
12	**5c**	Ph	CH_3	c-C_6H_{11}-	K_3PO_4	Toluene	90	30	**6c**	67
13	**5d**	Ph	CH_3	*i*-Pr	K_3PO_4	Toluene	90	20	**6d**	42
14	**5d**	Ph	CH_3	*i*-Pr	DMAP	Toluene	90	7	**6d**	54
15	**5e**	Ph	EtO	*i*-Pr	DMAP	Toluene	85	7	**6e**	56
16	**5e**	Ph	EtO	*i*-Pr	K_3PO_4	Toluene	90	15	**6e**	37
17	**5f**	MeO	MeO	c-C_6H_{11}-	DMAP	Toluene	70	30	**6f**	36
18	**5g**	MeO	MeO	*i*-Pr	DMAP	Toluene	70	30	**6g**	35
19	**5h**	EtO	EtO	*i*-Pr	DMAP	Toluene	85	22	**6h**	64
20	**5i**	EtO	EtO	c-C_6H_{11}-	DMAP	Toluene	85	22	**6i**	72
21	**5j**	*i*-PrO	*i*-PrO	*i*-Pr	DMAP	Toluene	70	20	**6j**	50
22	**5k**	*i*-PrO	*i*-PrO	c-C_6H_{11}-	DMAP	Toluene	70	20	**6k**	66
23	**5l**	CH_3	EtO	c-C_6H_{11}-	DMAP	Toluene	85	30	**6l**	55
24	**5m**	CH_3	CH_3	c-C_6H_{11}-	DMAP	Toluene	85	25	**6m**	62
25	**5n**	CH_3	CH_3	*i*-Pr	DMAP	Toluene	85	25	**6n**	49



Scheme 3. Preparation of 5-ethylidenehydantoin analogues.

diastereomers) via domino condensation/aza-Michael/N→O acyl migration (Scheme 2).[25] Finally, the obtained 1,3,5-trisubstituted hydantoins underwent dehydrogenation mediated by a PhI(OAc)/base system, and the 5-σ bonds of hydantoins were transformed into 5-π bonds, yielding tetrasubstituted 5-ethylidenehydantoin analogues (Scheme 3).

The reaction sequences are portrayed in Scheme 2.

Dehydrogenation of compound **5a** using $PhI(OAc)_2$ as the oxidant was selected as the benchmark reaction to explore the optimization of reaction conditions. Although our findings are tentative, negligible quantities of **6a** were observed in the absence of a base (Scheme 3, entry 1). Markedly superior results were observed when $KHCO_3$ was replaced with K_3PO_4 (entries 2–3). Switching the solvent to toluene resulted in an optimized 82% isolated yield for **6a** at 90 °C (entry 7). Changing the base from K_3PO_4 to DMAP also slightly increased product yields (entries 11–12, 13–14 and 15–16). After the judicious optimization of reaction parameters, we identified a protocol involving substrate and DMAP in toluene that was suitable for our purposes. Notably, identical reactivity was observed when both R_1 and R_2 were alkyl or alkoxy groups; however, a significant reduction in yields was observed when both R_1 and R_2 were alkyl or alkoxy groups rather than aryl groups. Unsurprisingly, *Z* and *E* isomers were obtained when R_1 and R_2 were not the same. Overall, 14 tetrasubstituted 5-ethylidenehydantoins were prepared, with yields ranging from 35% to 82% (Scheme 3). Our method expands the scope of available substrates and provides easy access to structurally diverse 5-ethylidenehydantoins that could be further functionalized. Approximately 20 min was required to complete the dehydrogenation. Further investigations aimed at testing the biological activities of related compounds are currently on-going in our laboratories.

Conclusion

In summary, we have developed a new route to synthesize tetrasubstituted 5-ethylidenehydantoins, which have an important, naturally occurring skeleton. Dehydrogenation was mediated by $PhI(OAc)_2$, which is a mild, highly stable oxidant with low toxicity. Our conditions enable a fast and convenient approach to hydantoins.

Experimental section

General methods

NMR spectra were recorded on Bruker DPX-400, DRX-500 and DRX-600 instruments. Chemical shifts were reported as δ values relative to internal chloroform (δ 7.26 for ^{1}H

NMR and 77.00 for ^{13}C NMR). High-resolution mass spectra (EI) were obtained on an API QStar Pulsar instrument. Infrared spectra were recorded on an FT-IR spectrometer. Silica gel (Wakogel, 300–400 mesh) was used for column chromatography. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials. Unless otherwise noted, materials obtained from commercial suppliers were used without additional purification. Toluene was distilled over CaH_2. THF (tetrahydrofuran) was distilled over sodium before use.

Key procedure for the preparation of 5-ethylidenehydantoin analogues (6a–6n)

Two equivalents of $PhI(OAc)_2$ and 3 equivalents of base were added to an 0.1 M solution of 1,3,5-trisubstituted hydantoin (**5a**–**n**) (1 equiv) in toluene. The reaction mixture was stirred at an appropriate temperature (~85 °C). After the starting material had been completely consumed (~20 min), water and EtOAc were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (three times). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography afforded the desired compound (**6a**–**n**).

Acknowledgements

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Disclosure statement

The authors declare no competing financial interests.

Supporting Information

Complete experimental details, ^1H and ^{13}C NMR spectra, HRMS and IR data, and information regarding materials can be found in the "Supplementary Content" section of this article's webpage.

References

[1] Hirai, K.; Fuchikami, T.; Fujita, A.; Hirose, H.; Yokota, M.; Nagato, S. Eur. Pat. Appl. E P 262,428,1988; *Chem. Abstr.* **1988**, *109*, 93010k.
[2] Cremlyn, R. J. W.; Jethwa, S.; Joiner, G.; White, D. *Relat. Elem.* **1988**, *36*, 99.
[3] Thenmozhiyal, J. C.; Wong, P. T.-H.; Chui, W.-K. *J. Med. Chem.* **2004**, *47*, 1527.
[4] Carmi, C.; Cavazzoni, A.; Zuliani, V.; Lodola, A.; Bordi, F.; Plazzi, P. V.; Alfieri, R. R.; Petronini, P. G.; Mor, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4021.
[5] Mudit, M.; Khanfar, M.; Muralidharan, A.; Thomas, S.; Shah, G. V.; Soest, R. W. M. V.; Sayed, K. A. E. *Bioorg. Med. Chem.* **2009**, *17*, 1731.
[6] Khanfar, M. A.; Asal, B. A.; Mudit, M.; Kaddoumi, A.; Sayed, K. A. E. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 6032.
[7] Balansa, W.; Islam, R.; Gilbert, D. F.; Fontaine, F.; Xiao, X.; Zhang, H.; Piggott, A. M.; Lynch, J. W.; Capon, R. *J. Bioorg. Med. Chem. Lett.* **2013**, *21*, 4420.
[8] (a) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143. (b) Tutino, F.; Posteri, H.; Borghi, D.; Quartieri, F.; Mongelli, N.; Papeo, G. *Tetrahedron*, **2009**, *65*, 2372.
[9] Sosa, A. C. B.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **2002**, *67*, 4498.

[10] Cachet, N.; Genta-Jouve, G.; Regalado, E. L.; Mokrini, R.; Amade, P.; Culioli, G.; Thomas, O. P.; *J. Nat. Prod.* **2009**, *72*, 1612.
[11] Watterson, S. H.; Xiao, Z.; Dodd, D. S.; Tortolani, D. R.; et al. *J. Med. Chem.* **2010**, *53*, 3814.
[12] Potin, D.; Launay, M.; Monatlik, F.; Malabre, P.; Fabreguettes, M.; et al. *J. Med. Chem.* **2006**, *49*, 6946.
[13] He, X.-Y.; Zou, P.; Qiu, J.; Hou, L.; Jiang, S.; Liu, S.; Xie, L. *Bioorg. Med. Chem. Lett.* **2011**, *19*, 6726.
[14] Warner-Lambert Co. 1-Substituted-phenyl-4-alkyl hydantoinpiperizine compounds as anti-hypertensive agenta. U.S. Pat. 4,462,198A, 1984; *Chem. Abstr.* **1986**, *101*, 38476b.
[15] Cortes, S.; Liao, Z.-K.; Watson, D.; Kohn, H. *J. Med. Chem.* **1985**, *28*, 601.
[16] Rizzi, J. P.; Schnur, R. C.; Hutson, N. J.; Kraus, K. G.; Kelbaugh, P. R. *J. Med. Chem.* **1989**, *32*, 1208.
[17] Barraclough, P.; Caldwell, A. G.; Harris, C. J.; Jackson, W. P.; Whittle, B. J. R. *J. Chem. SOC., Perkin Trans. 1.* **1989**, *10*, 1815.
[18] Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.* **1988**, *31*, 230.
[19] Bahy, A.; Kacem, Y.; Hassine, B. B. *Synth. Commun.* **2010**, *40*, 1377.
[20] Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369.
[21] Sankhavasi, W.; Kohmoto, S.; Yamamoto, M.; Nishio, T.; Iida, I.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 935.
[22] Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K. *J. Org. Chem.* **1991**, *56*, 6897.
[23] Mathur, N. C.; Wong, S. K.; Shechter, H. *Tetrahedron Lett.* **2003**, *44*, 5141.
[24] Palacios, F.; Legido, M.; Heredia, I. P.; Ezpeleta, J. M.; Rubiales, G. *Heterocycles.* **2001**, *55*, 1641.
[25] Volonterio, A.; Arellano, C. R. D.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 2161.
[26] Törmäkangas, O. P.; Toivola, R. J.; Karvinen, E. K.; Koskinen, A. M. P. *Tetrahedron.* **2002**, *58*, 2175.
[27] Goh, K. K. K.; Kim, S.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 4818.
[28] Y. Zhao, X. Jiang, Y.-Y. Yeung. *Angew. Chem. Int. Ed. Engl* **2013**, *52*, 8597.
[29] Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679.
[30] Lenz, G. R.; Lessor, R. A. *Org. Synth.* **1998**, *9*, 268.
[31] Maggi, R.; Bosica, G.; Gherardi, S.; Oro, C.; Sartori, G.; *Green Chem.* **2005**, *7*, 182.