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Preparation of Hydantoins by Catalytic Oxidative Carbonylation of α-Amino Amides

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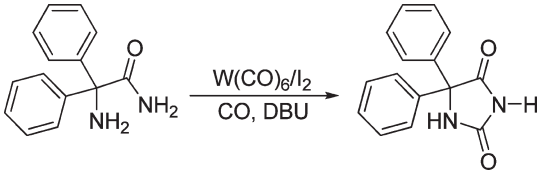
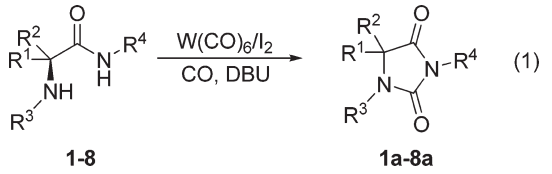


Hydantoins can be synthesized from the corresponding amino amides employing oxidative catalytic carbonylation using $W(CO)_6$ as the catalyst, I_2 as the oxidant, CO as the carbonyl source, and DBU as base. Secondary amides afford the hydantoins in good to excellent yields, which decrease as the steric bulk of the *N*-alkyl substituent increases.

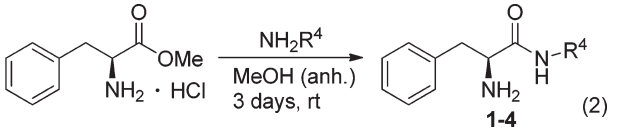
Hydantoins have been of considerable interest as they are frequently found as crucial moieties in many biologically active molecules. More specifically, hydantoins substituted at C-5 constitute an important class of heterocycles in medicinal chemistry since derivatives are associated with a wide range of biological properties including anticonvulsant,[1] antidepressant,[2,3] antiviral[2,3] and platelet inhibitory activities.[4]

Various synthetic methods exist to afford hydantoins from diverse starting materials. Classical routes include reaction of ureas with carbonyl compounds[5] and the Bucherer−Bergs route involving inorganic cyanide with carbonyl compounds.[6] A variety of additional methods utilize both solution-phase[7−12] and solid-phase synthesis[5,13] to prepare substituted hydantoins. The use of phosgene[13] and its derivatives has also been reported.[12,14]

To address various safety and environmental concerns[15] associated with the use of phosgene and its derivatives, we have previously reported the use of $W(CO)_6$-catalyzed oxidative carbonylation to afford cyclic ureas from primary and secondary diamines.[16−21] Herein, we would like to report the synthesis of a series of C-5 substituted hydantoins starting from enantiomerically pure α-amino amides via $W(CO)_6$-catalyzed carbonylation using I_2 as oxidant (eq 1, Table 1).



Amino amides **1**−**4** were synthesized by reaction of the corresponding amino acid methyl ester hydrochloride with an amine[12] (eq 2, Table 2). After purification, **1** was chosen as substrate for optimization of the carbonylation conditions. Initial attempts using conditions previously successful with amino alcohol substrates[21] failed to generate any observable hydantoin. Failure to form hydantoin **1a** (eq 1) under the optimal carbonylation conditions for amines is not surprising, however, as the amide moiety of **1** is much less nucleophilic than the substrates we have previously studied.



To overcome this problem, higher temperatures, longer reaction times, other solvents, and a variety of bases were studied (Table 3).[22] The critical variable was the choice of base. Entry 10 shows the optimized conditions utilizing DBU

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TABLE 1. Substitution Patterns of 1−8 and 1a−8a

compound	R^1	R^2	R^3	R^4
1	CH_2Ph	H	H	CH_3
2	CH_2Ph	H	H	CH_2CH_3
3	CH_2Ph	H	H	$(CH_3)_2CH$
4	CH_2Ph	H	H	CH_2Ph
5	CH_2OH	H	H	CH_2Ph
6	CH_2Ph	H	CH_2Ph	H
7	Ph	Ph	H	CH_2Ph
8	Ph	Ph	H	H

TABLE 2. Yields of 1−4 from the Amino Acid Methyl Ester

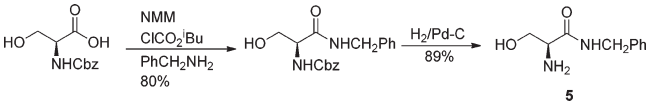
compound	yield (%)
1	90
2	82
3	74
4	84

TABLE 3. Optimization of Conditions for $W(CO)_6/I_2$ Carbonylation of α-Amino Amide 1

entry	time (h)	CO (atm)	temp (°C)	base/ equiv	solvent[a]	yield (%)
1	24	80	45	Py/2	CH_2Cl_2	0
2	36	90	55	Py/2	CH_2Cl_2	40
3	45	80	25	Py/2	CH_2Cl_2	0
4	36	90	50	K_2CO_3	CH_2Cl_2/H_2O	20
5	42	90	50	DMAP/2	CH_2Cl_2	0
6	36	85	45	DMAP/3	toluene	0
7	36	85	45	DMAP/3	CH_2Cl_2/H_2O	50
8	36	85	45	DMAP/4	CH_2Cl_2/H_2O	50
9	48	85	45	DMAP/4	CH_2Cl_2/H_2O	trace
10	36	80	45	DBU/4	DCE	72

[a]The solution concentration of entry 1 was 4 M (0.87 mL of solvent); all others were conducted at 0.031 M (35 mL of solvent).[22]

SCHEME 1. Synthesis of 5



as the base and 36 h reaction time. Product decomposition was observed at longer reaction times.

Amino amides **5**−**9** could not be obtained in acceptable quantities via the route in eq 2, so alternative methods were employed for their synthesis. Substrate **5** was prepared using a mixed anhydride coupling procedure[23] (Scheme 1), affording a yield of 71% from the amino acid.

The secondary amino amide **6** (Scheme 2) was synthesized in an overall yield of 72% according to literature precedent by condensation of L-phenylalanamide with benzaldehyde followed by reduction with $NaBH_4$.[24] Compounds **7** and **8** were both synthesized from the N-Boc-protected amino acid **9**. Conversion of **9** to **7** was then realized in 81% yield utilizing a benzotriazole-mediated coupling.[25] Attempts to

SCHEME 2. Synthesis of 6−9

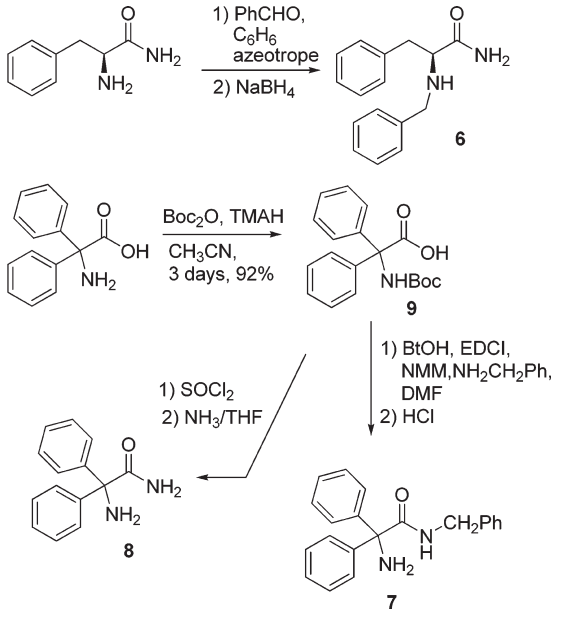


TABLE 4. Yields of Hydantoins 1a−8a from $W(CO)_6/I_2$ Carbonylation of 1−8

α-amino amide	product	yield (%)
1	**1a**	73
2	**2a**	61
3	**3a**	trace
4	**4a**	75
5	**5a**	50
6[a]	**6a**	41
7[a]	**7a**	11
8[a]	**8a**	64

[a]Conditions for carbonylation were 1.1 equiv of DBU, 35 °C, 24 h with CH_2Cl_2 as solvent. Other conditions are as reported for optimization of **1** to **1a**.

use **7** as a precursor to **8** failed as we could not find conditions to remove the benzyl unit by hydrogenation. Amino amide **8** was instead synthesized by treatment of the Boc-protected amino acid **9** with $SOCl_2$ followed by addition of a saturated solution of ammonia in THF. This procedure proved fortuitous as it also resulted in the removal of the Boc protecting group to afford **8** in an overall yield of 88%.

Substrates **1**−**8** were then carbonylated using the conditions optimized for the conversion of **1** to **1a** (Table 4). Hydantoins **1a**−**8a** were obtained in moderate to good yields. The yields of **1a**−**4a** from amino amides **1**−**4** show the effects of steric variation in the amide *N*-alkyl group on the ring closure. The yields were highest from substrates **1**, **2**, and **4** (R^4 = Me, Et, Bn), which have no branching at the α-carbon of the substituent. The effect of a secondary alkyl substituent is seen with **3** ($R^4 = {}^i$Pr), for which the hydantoin product **3a** was produced in only trace quantities. Similar effects have been observed previously in the carbonylation of secondary diamines containing these *N*-alkyl substituents.[17]

Compound **6**, the constitutional isomer of **4**, afforded hydantoin **6a** in 41% yield under slightly different conditions. Although **6** is more nucleophilic than **4**, it illustrates the effect that steric bulk at the amine nitrogen has on this system as **6a** could only be obtained in about half the yield of **4a**. Hydantoin **8a** is the pharmaceutical phenytoin, which is

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an anticonvulsant used in the treatment of seizures. It was obtained in an optimized yield of 64% but required a switch to DCM as the solvent as an unidentified oligomerization occurred in DCE. Although amines are known to react with chlorinated solvents,[26] no products of reaction with DCE were observed, and we attribute the higher yields of hydantoins in DCM to higher solubility of the substrate. Unfortunately, decomposition of **8** to produce benzophenone is competitive with product formation, even when milder conditions using less base and much shorter reaction times are employed. Hydantoin **7a** could be obtained in 11% yield, but decomposition of **7** to benzophenone appears to be faster than carbonylation. One possible explanation for the lower yields of hydantoins from primary amides as compared to their secondary counterparts is that decomposition of the starting material is competitive with product formation.

Despite the lower nucleophilicity of the amide nitrogen compared to that of the amine, no symmetrical acyclic ureas were detected in reaction mixtures from any of the substrates. The mechanism for carbonylation of α-amino amides **1**−**8** has not been elucidated. Our previous studies of higher valent tungsten catalysts suggest the intermediacy of either free or coordinated isocyanates,[27] a mechanism that is also precedented in other literature.[28] This mechanism is possible for most of the α-amino amides studied here. However, the secondary amino amide **6** cannot form an isocyanate intermediate but still yields hydantoin **6a**, ruling out the intermediacy of an isocyanate for that particular substrate.

Other group VI metal carbonyls such as chromium hexacarbonyl and molybdenum carbonyl have been previously investigated as catalysts for the oxidative carbonylation of amines.[17] However, tungsten hexacarbonyl afforded higher yields of ureas from primary and secondary aliphatic amines. Similar experiments were carried out for the amino amide substrate **1** using $Mo(CO)_6$ and $Cr(CO)_6$ as catalysts. However, the yield obtained for the hydantoin **1a** was 20% in the case of Mo, while the Cr catalyst produced an inseparable mixture.

In summary, we have shown that $W(CO)_6$-catalyzed oxidative carbonylation of amino amides results in moderate-to-good yields of hydantoins. Steric hindrance at the amine nitrogen has an effect on the yield, and decomposition of the substrate is competitive with product formation in a few cases. The use of our catalytic oxidative carbonylation reaction provides an alternative to other existing methodologies for hydantoin synthesis and can successfully yield hydantoins from primary-amino-secondary amides in good yields.

Experimental Section

General. All reactions were conducted under an inert argon atmosphere using oven-dried glassware unless otherwise noted. All column chromatography used Fisher brand 230−400 mesh silica gel. Reagents and solvents were purchased and used without further purification. **Caution:** Adequate ventilation and shielding equipment are required when using high pressure CO.

***N*-Benzyl-α,α-diphenylglycamide (7).** The Boc-protected amino acid **9** was converted to the amide via benzotriazole-mediated coupling.[25] After workup, the mixture was then deprotected using 5 molar equiv of 4.0 M HCl in dioxane and stirred overnight. The resulting mixture was purified on silica using a solvent gradient from DCM to 90:10 DCM/MeOH to afford **7** in 72% yield. The product was identified by comparison to literature data.[29]

α,α-Diphenylglycamide (8). The Boc-protected amino acid **9** (1.00 g, 3.18 mmol) was dissolved in 20 mL of DCM and brought to reflux under Ar, according to a procedure adapted from the literature.[30] Then $SOCl_2$ (1.13 g, 9.54 mmol) was added, and the mixture continued to reflux for 3 h. After cooling, the acid chloride solution was evaporated in vacuo, and 50 mL of THF saturated in ammonia was slowly added. The reaction mixture was stirred overnight. The excess ammonia was removed by sparging with N_2, and the concentrate was dissolved in DCM and washed once with H_2O. The organics were separated and dried over $MgSO_4$. The reaction mixture was purified by column chromatography (95:5 DCM/MeOH) on silica to afford **8** in 95% yield. The compound was identified by comparison to literature data.[31]

***N*-Boc-α,α-Diphenylglycine (9).** The commercially available α,α-diphenylglycine (2.26 g, 10 mmol) was slurried in 80 mL of acetonitrile and dissolved in a minimum amount of 25% (w/w) tetramethylammonium hydroxide in water. Di-*tert*-butyldicarbonate (5.00 g, 25 mmol) was added over a 3 day period and allowed to stir for a total of 4 days until TLC indicated that the reaction was complete. The mixture was then concentrated under reduced pressure and dissolved in 150 mL of EtOAc and acidified to pH 3−4 using 1.0 M HCl. The organics were separated, and the aqueous material was extracted twice with EtOAc. The organics were combined, washed with brine, and then dried over $MgSO_4$. The product was obtained in 92% yield following column chromatography (97:3 DCM/MeOH) on silica, and the pure compound was identified by comparison to literature data.[25] Yield, 92%.

General Procedure A for Catalytic Carbonylation of 1−5.[22] To a 300 mL glass lined Parr high-pressure vessel containing 35 mL of 1,2-dichloroethane were added α-amino amide **1** (400 mg, 2.2 mmol), $W(CO)_6$ (56 mg, 0.16 mmol), I_2 (396 mg, 1.56 mmol), and DBU (1.34 mL, 8.96 mmol). The vessel was then charged with 80 atm CO and heated to 45 °C for 36 h with constant stirring. The pressure was released, and 15 mL of water was added. The organics were then separated and washed separately with Na_2SO_3 and with 0.1 N HCl. The aqueous layer was extracted with EtOAc (20 mL × 4). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified via column chromatography on silica using DCM/EtOAc (80:20) to afford hydantoin **1a** in 72% yield. The same procedure was applied to prepare hydantoins **2a**−**5a**, which were identified by comparison to literature data.[12,32,33]

General Procedure B for Catalytic Carbonylation of 6−8. To a 300 mL glass lined Parr high-pressure vessel containing 20 mL of DCM were added α-amino amide **8** (250 mg, 1.1 mmol), $W(CO)_6$ (29 mg, 0.081 mmol), I_2 (195 mg, 0.77 mmol), and DBU (0.184 mL, 1.22 mmol). The vessel was then charged with 80 atm CO and heated to 35 °C for 24 h with constant stirring. The pressure was released, and 20 mL of 95:5 (DCM/MeOH) was added. The organics were then immediately washed with Na_2SO_3 and separated. The aqueous layer was then extracted

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with ethyl acetate (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The resulting residue was purified via column chromatography on silica using DCM/EtOAc (80:20) to afford hydantoin **8a** in 64% yield. Identification of **8a** was made by comparison to a commercially available sample. The same procedure was applied to prepare hydantoins **6a** and **7a**, which were identified by comparison to literature data.[34,35]

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Supporting Information Available: ^{1}H NMR spectra of compounds **7**−**9**, **1a**, **2a**, and **4a**−**8a**. Previously unreported spectral data (^{1}H NMR, ^{13}C NMR and IR) for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.