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Nickel-Catalyzed Synthesis of 1,3,5-Trisubstituted Hydantoins from Acrylates and Isocyanates

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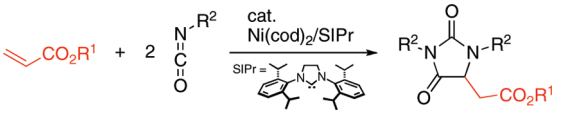
ABSTRACT



One molecule of acrylate reacts with two molecules of isocyanate in the presence of a nickel(0)/SIPr catalyst to give a 1,3,5-trisubstituted hydantoin. Two processes operate in sequence, the first, regioselective formation of *N*-substituted fumaramate from acrylate and isocyanate and, the second, ring closure of the fumaramate with incorporation of another molecule of isocyanate.

A hydantoin (imidazolidine-2,4-dione) skeleton[1] is an important structural motif found in a number of pharmaceutically active compounds,[2] such as phenytoin and fosphenytoin which are in practical use for the treatment of epilepsy. In addition, substituted hydantoins act as valuable intermediates for the synthesis of enantiomerically pure amino acids through dynamic kinetic resolution using hydantoinase biocatalysis.[3] Therefore, the development of efficient methods for rapid construction of hydantoin skeletons from simple and inexpensive starting materials is highly desired. Various preparative methods based on transition-metal catalysts have been reported. A formal intermolecular [2 + 2 + 1] cycloaddition reaction of one molecule of phenylacetylene and two molecules of isocyanate is catalyzed by iron,[4] ruthenium,[5] and manganese[6] complexes, leading to the formation of 5-benzylidene-1,3-disubstituted hydantoins. A copper-catalyzed C−H α-amination reaction of esters with di-*tert*-butyldiaziridinone affords 1,3,5-trisubstituted hydantoins.[7] A palladium-catalyzed carbonylation reaction of aldehydes with ureas and carbon monoxide furnishes 5-, 3,5-, and 1,3,5-substituted hydantoins.[8] However, there has been no report on the hydantoin synthesis starting from acrylates and isocyanates. We now report the synthesis of 1,3,5-trisubstituted hydantoins[9] from one molecule of acrylate and two molecules of isocyanate by use of nickel catalysis.

(1) For a review of hydantoin chemistry, see: Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int.* **2004**, *36*, 391.

(2) (a) Last-Barney, K.; Davidson, W.; Cardozo, M.; Frye, L. L.; Grygon, C. A.; Hopkins, J. L.; Jeanfavre, D. D.; Pav, S.; Qian, C.; Stevenson, J. M.; Tong, L.; Zindell, R.; Kelly, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 5643. (b) Stilz, H. U.; Guba, W.; Jablonka, B.; Just, M.; Klingler, O.; König, W.; Wehner, V.; Zoller, G. *J. Med. Chem.* **2001**, *44*, 1158. (c) Somsák, L.; Kovács, L.; Tóth, M.; Osz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843. (d) Thenmozhiyal, J. C.; Wong, P. T.-H.; Chui, W.-K. *J. Med. Chem.* **2004**, *47*, 1527. (e) Muccioli, G. G.; Fazio, N.; Scriba, G. K. E.; Poppitz, W.; Cannata, F.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 417.

(3) Burton, S. G.; Dorrington, R. A. *Tetrahedron: Asymmetry* **2004**, *15*, 2737.

(4) Ohshiro, Y.; Kinugasa, K.; Minami, T.; Agawa, T. *J. Org. Chem.* **1970**, *35*, 2136.

(5) Süss-Fink, G.; Schmidt, G. F.; Herrmann, G. *Chem. Ber.* **1987**, *120*, 1451.

(6) Kuninobu, Y.; Kikuchi, K.; Takai, K. *Chem. Lett.* **2008**, *37*, 740.

(7) Zhao, B.; Du, H.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220.

(8) Beller, M.; Eckert, M.; Moradi, W. A.; Neumann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1454.

(9) For recent examples of the synthesis of 1,3,5-substituted hydantoins without the use of transition-metal catalysts, see: (a) Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, *62*, 3230. (b) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090. (c) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603. (d) Hulme, C.; Ma, L.; Romano, J. J.; Morton, G.; Tang, S.-Y.; Cherrier, M.-P.; Choi, S.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1889. (e) Zhang, W.; Lu, Y. *Org. Lett.* **2003**, *5*, 2555. (f) Ignacio, J. M.; Macho, S.; Marcaccini, S.; Pepino, R.; Torroba, T. *Synlett* **2005**, 3051. (g) Volonterio, A.; de Arellano, C. R.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 2161. (h) Olimpieri, F.; Volonterio, A.; Zanda, M. *Synlett* **2008**, 3016. (i) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Nicolini, S.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2011**, *13*, 353.

(10) Miura, T.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 15836.

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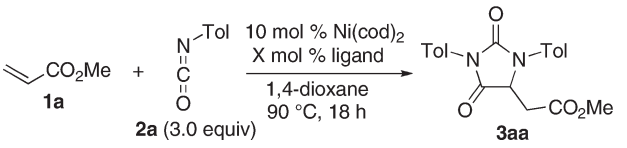
Table 1. Optimization of Reaction Conditions[a]

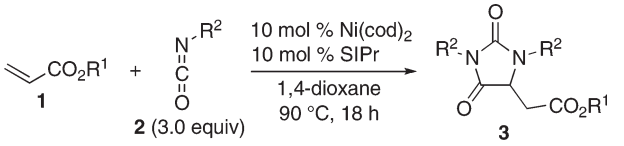


entry	ligand	*X*/mol %	NMR yield/%[b]
1	PCy_3	20	6
2	PPh_3	20	0
3	Dppe	10	1
4	IMes	10	8
5	SIMes	10	82
6	IPr	10	83
7	SIPr	10	83 (79)

[a] All reactions were carried out on a 0.4 mmol scale. [b] ^{1}H NMR yield using $CHCl_2CHCl_2$ as an internal standard with isolated yield in parentheses. Abbreviations: IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene.

We have recently developed[10] a highly enantioselective [2 + 2 + 2] cycloaddition reaction of one molecule of allene and two molecules of isocyanate using a nickel(0)/(*S*,*S*)-*i*-Pr-FOXAP[11] catalyst. This method allowed for facile preparation of enantiomerically enriched dihydropyrimidine-2,4-diones. On the other hand, it has been reported that the [2 + 2 + 2] cycloaddition reaction of one molecule of methyl acrylate and two molecules of phenyl isocyanate in the presence of a nickel(0)/PCy_3 catalyst affords 1,3-diphenyl-6-methoxycarbonyldihydropyrimidine-2,4-dione in 60% yield.[12] As a continuation of our study on metal-catalyzed asymmetric cycloaddition reactions of isocyanates, we next examined the asymmetric version using chiral ligands in a reaction of methyl acrylate (**1a**) and 4-tolyl isocyanate (**2a**). When **1a** (1.0 equiv) was treated with **2a** (3.0 equiv) in the presence of a nickel(0)/(*S*,*S*)-*i*-Pr-FOXAP[11] catalyst which was effective for the allene/isocyanate cycloaddition,[10] no cycloadduct was obtained. When (*S*,*S*)-CHIRAPHOS[11] was used as the ligand, 8% of a 1:2 acrylate/isocyanate cycloadduct was obtained (0% ee). The structure of the cycloadduct was determined to be 1,3-ditolyl-5-(methoxycarbonylmethyl)hydantoin (**3aa**) having a five-membered ring, rather than 1,3-ditolyl-6-methoxycarbonyldihydropyrimidine-2,4-dione having a six-membered ring, by derivatization to the ethoxycarbonyl compound which is known in literature.[9g] This unexpected result prompted us to re-examine the nickel-catalyzed reaction of **1a** with **2a** using achiral ligands as shown in Table 1.[13] The cycloadduct **3aa** was scarcely obtained when phosphine ligands such as PPh_3, PCy_3, and dppe were used (entries 1−3). On the contrary, the use of *N*-heterocyclic carbene (NHC) ligands afforded fairly good results (entries 4−7).[14] Among them, SIPr most effectively promoted the reaction to give **3aa** in 79% isolated yield.

Table 2. Ni-Catalyzed Synthesis of 1,3,5-Trisubstituted Hydantoins **3** from Acrylates **1** and Isocyanates **2**[a]



entry	**1** (R^1)	**2** (R^2)	**3**	yield/%[b]
1	**1a** (Me)	**2b** (Ph)	**3ab**	75
2	**1a**	**2c** (3-Tol)	**3ac**	77[c]
3	**1a**	**2d** (2-Tol)	**3ad**	68
4	**1a**	**2e** (4-MeO-C_6H_4 (PMP))	**3ae**	72[c]
5	**1a**	**2f** (4-Cl-C_6H_4)	**3af**	74
6	**1a**	**2g** (4-MeO_2C-C_6H_4)	**3ag**	67[c]
7	**1a**	**2h** (4-$CH_3C(O)$-C_6H_4)	**3ah**	65[c,d]
8	**1a**	**2i** (4-CF_3-C_6H_4)	**3ai**	72
9	**1b** (Et)	**2a** (4-Tol)	**3ba**	88
10	**1c** (Bn)	**2a**	**3ca**	81
11	**1d** (*i*-Pr)	**2a**	**3da**	78
12	**1e** (*t*-Bu)	**2a**	**3ea**	35[c]

[a] The reaction was carried out with **1** (0.4 mmol), **2** (1.2 mmol), $Ni(cod)_2$ (10 mol %), and SIPr (10 mol %) in 1,4-dioxane (2.0 mL) at 90 °C for 18 h, unless otherwise noted. [b] Isolated yield. [c] 110 °C. [d] Using 1,4-dioxane (4.0 mL).

The results obtained with various combinations of acrylates **1** and isocyanates **2** using a nickel(0)/SIPr catalyst are summarized in Table 2. The reaction of **1a** with a sterically and electronically diverse array of aryl isocyanates **2b**−**i** proceeded well to give the corresponding 1,3,5-trisubstituted hydantoins **3ab**−**ai** in yields ranging from 65% to 77% (entries 1−8). In contrast, alkyl isocyanates gave inferior results. The reaction of **1a** with *n*-hexyl isocyanate or benzyl isocyanate produced large amounts of isocyanate oligomers together with a trace amount of the corresponding 1,3,5-trisubstituted hydantoin. Cyclohexyl isocyanate and *tert*-butyl isocyanate gave no desired products either. Both primary and secondary alkyl acrylates **1b**−**d** readily reacted with **2a** to afford the corresponding hydantoins **3ba**−**da** in good yield (entries 9−11), whereas the reaction of *tert*-butyl acrylate was relatively sluggish to give the product **3ea** only in 35% yield (entry 12). It was noteworthy that a spirocyclic hydantoin

(11) Abbreviations: (*S*,*S*)-*i*-Pr-Foxap = (*S*,*S*)-[2-(4′-isopropyloxazolin-2′-yl)ferrocenyl]diphenylphosphine. See: Miyake, Y.; Nishibayashi, Y.; Uemura, S. *Synlett* **2008**, 1747. (*S*,*S*)-CHIRAPHOS = (2*S*,3*S*)-bis(diphenylphosphino)butane.

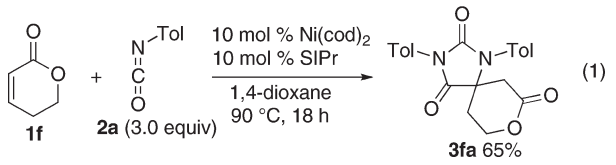
(12) Hoberg, H.; Guhl, D. *J. Organomet. Chem.* **1989**, *375*, 245.

(13) When the reaction of **1a** with **2b** was carried out under the reported conditions[12] in our laboratory, 1,3-diphenyl-5-(methoxycarbonylmethyl)hydantoin (**3ab**) was produced in 2% NMR yield and no formation of 1,3-diphenyl-6-methoxycarbonyldihydropyrimidine-2,4-dione was observed in ^{1}H NMR spectra of the reaction mixture.

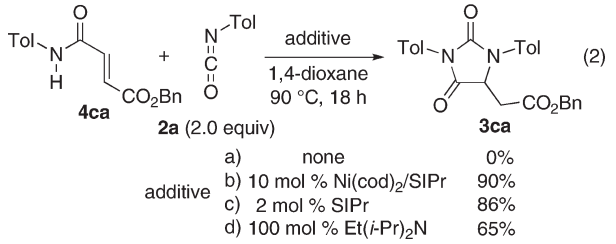
(14) The asymmetric version using chiral NHC ligands was briefly examined. However, no asymmetric induction was observed.

(15) For β-hydride elimination of a five-membered ring azanicklacycle in *anti* mode, see: Hoberg, H.; Nohlen, M. *J. Organomet. Chem.* **1990**, *382*, C6.

skeleton was also constructed by using 5,6-dihydro-2*H*-pyran-2-one (**1f**) as the substrate (eq 1).[15]



When the nickel-catalyzed reaction of **1c** (1.0 equiv) with **2a** (3.0 equiv) at 90 °C was quenched after 30 min, the fumaramate **4ca** was isolated in 33% yield in addition to **3ca** (20% yield). The isolated fumaramate **4ca** was treated with the isocyanate **2a** (2.0 equiv) in the absence and presence of a nickel(0)/SIPr catalyst (eq 2).



Whereas essentially no reaction was observed in the absence of a $Ni(cod)_2$/SIPr catalyst, **3ca** was formed in 90% yield in the presence of a $Ni(cod)_2$/SIPr catalyst (10 mol %). Furthermore, the reaction proceeded in the presence of only SIPr (2 mol %). Even $Et(i\text{-}Pr)_2N$ (100 mol %) mediated a cyclization reaction of **4ca** with **2a**.

The time-dependent change of the reaction mixture of **1c** with **2a** was followed by measuring ^1H NMR spectra at 10 min intervals (Figure 1). An initial increase of **3ca** was slower than the decrease of **1c**. On the other hand, the fumaramate **4ca** increased up to a 52% yield after 40 min and then gradually decreased. These results indicated that the reaction proceeds *via* the formation of *N*-substituted fumaramate as the key intermediate.

On the basis of these results, we propose a mechanism for the production of 1,3,5-trisubstituted hydantoins **3** from acrylates **1** and isocyanates **2** as depicted in Scheme 1. Initially, the oxidative cyclization on nickel(0) occurs with a heteropair of **1** and **2** to give a five-membered ring azanickelacycle **A**,[12] with which the ester group is bound to the carbon α to nickel.[16] We assume that a partial negative charge developing on the α carbon is stabilized by the ester substituent.[17] Subsequent *β*-hydride elimination and reductive elimination results in the formation of *N*-substituted fumaramates **4**. Next, the amide group of **4** is deprotonated by the NHC ligand (SIPr).[18,19]

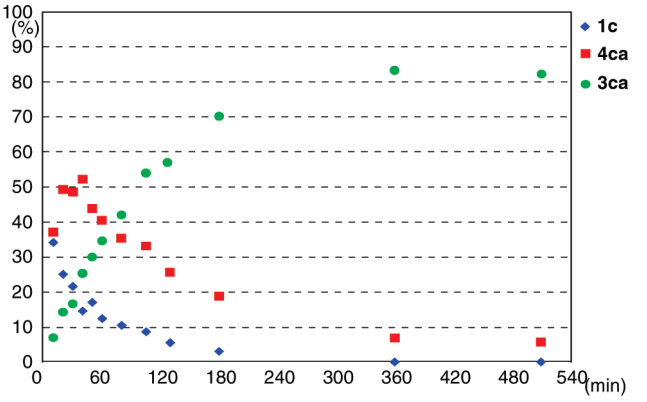
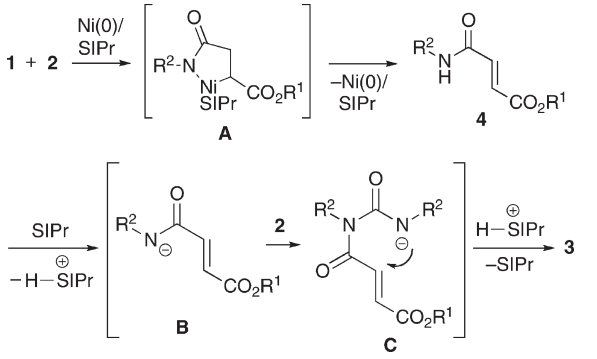


Figure 1. Time-dependent change of the reaction mixture of **1c** with **2a** using a nickel(0)/SIPr catalyst. The yield of the corresponding compounds (**1c**, blue diamond; **4ca**, red square; and **3ca**, green circle) was determeined by ^1H NMR spectra using 2-methoxynaphthalene as an internal standard.

The resulting amide anion adds to another molecule of **2** to afford the anionic intermdiate **C**. Subsequent ring closure by conjugate addition in a five-*exo* mode furnishes hydantoins **3**.[20]

Scheme 1. Proposed Reaction Mechanism



Next, we examined a two-step procedure for preparation of a hydantoin which incorporated two different isocyanates. The isolated fumaramate **4ca**[21] was treated with 4-methoxyphenyl (PMP) isocyanate (**2e**, 2.0 equiv) in the presence of SIPr (5 mol %), and 1-(4-methoxyphenyl)-3-tolyl-5-(benzyloxycarbonylmethyl)hydantoin **3cae** was obtained in 86% yield (eq 3). This two-step procedure would significantly expand the structural variation of the

(16) Oxidative cyclization of 1-octene and cyclohexyl isocyanate catalyzed by a nickel(0)/IPr complex forms five-membered ring azanickelacycle, the alkene substituent (a hexyl group) of which is bound to a carbon *β* to nickel. Schleicher, K. D.; Jamison, T. F. *Org. Lett.* **2007**, *9*, 875.

(17) For related stablization, see: Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098.

(18) It has been reported that $Ni(cod)_2$ and IPr exist in equiblium with $Ni(IPr)_2$ and COD (K_{eq} = 1). Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188.

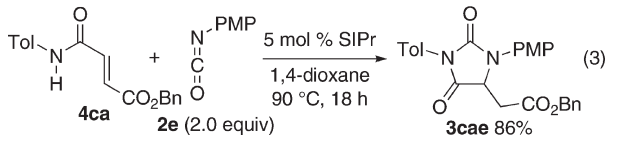
(19) For an example of NHC acting as a base, see: Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 13179.

(20) Another mechanism consisting of intermolecular addition of NHC to isocyanate followed by conjugate addition of the resulting nitrogen anion to **4** and subsequent ring closure is also conceivable. For intermolecular addition of NHC to isocyanate, see: Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679.

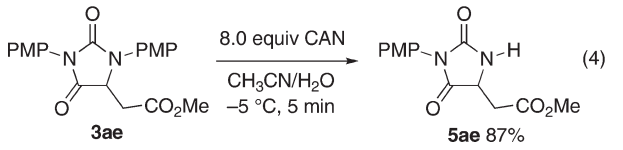
(21) *N*-Substituted fumaramates can be also prepared by half-esterification of fumaric acid with alcohols, followed by amidation with aniline derivatives. See the Supporting Information for details.

(22) Yamauchi, M.; Morimoto, M.; Miura, T.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 54.

produced hydantoins.



The removal of the PMP groups was examined. When **3ae** was treated with ceric ammonium nitrate (CAN) at −5 °C for 5 min,[22] the PMP group at the N1-position was selectively removed to give 3,5-disubstituted hydantoin **5ae** in 87% yield (eq 4).[7] The PMP group at the N3-position remained even under more forcing conditions (40 °C, 20 min).



In summary, a new synthetic route of 1,3,5-trisubstituted hydantoins starting from acrylates and isocyanates has been developed using a nickel(0)/SIPr catalyst. *N*-Substituted fumaramate is initially generated as the key intermediate, which then undergoes ring construction with another molecule of isocyanate in a one-pot sequence.

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Supporting Information Available. Experimental details and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.