Pergamon

Tetrahedron Letters 42 (2001) 3545–3547

TETRAHEDRON LETTERS

Lanthanide triflate catalyzed 1,3-dipolar cycloaddition reactions: stereoselective synthesis of indenoisoxazolidines

David A. Nugiel*

DuPont Pharmaceuticals, Box 80336, Wilmington, DE 19880-0336, USA

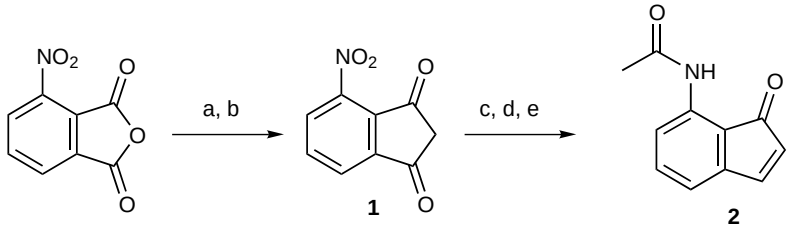
Received 28 February 2001; revised 23 March 2001; accepted 26 March 2001

Abstract—Substituted indenones reacted smoothly with a variety of in situ generated nitrones in the presence of lanthanide triflates to give exclusive *exo* 1,3-dipolar cycloaddition products in high yield. Judicious choice of the nitrone substituents allowed for further modification of the indenoisoxazolidine core to the corresponding indenoisoxazoline and indenoisoxazole analogs in high yield. © 2001 Published by Elsevier Science Ltd.

There have been several recent reports on the properties and synthesis of indenoisoxazolidines.[1] Synthetic approaches to these ring systems rely primarily on thermal 1,3-dipolar cycloadditions of nitrones with a partnering olefin. Few examples take advantage of Lewis acid catalyzed 1,3-dipolar cycloadditions as a means of preparing these ring systems. There have also been several recent disclosures of lanthanide triflate catalyzed 1,3-dipolar cycloaddition reactions as a means to prepare a variety of substituted isoxazoline systems.[2] These reports demonstrate the high *endo* selective nature of this reaction in addition to the mild reaction conditions for preparing the desired targets.

We recently disclosed a novel series of cyclin dependent kinase inhibitors based on an indenopyrazole core.[3] Preparing indenoisoxazoles was a logical extension of the SAR. To this end we explored new methods for preparing indenoisoxazoles mediated by lanthanide triflate catalyzed 1,3-dipolar cycloaddition reactions. We were able to apply this useful reaction towards the preparation of indenoisoxazolidines with exclusive *exo* selectivity. In addition, we could further manipulate the isoxazolidine core and prepare isoxazolines and isoxazoles depending on the reaction sequence chosen. We found the reaction between substituted indenones and in situ generated nitrones to proceed efficiently and in high yield to give the corresponding indenoisoxazolidines.

Preparation of the starting indenone system is shown in Scheme 1. Condensing 3-nitrophthalic anhydride with ethylacetoacetate and acetic anhydride gave the desired carbethoxyindanedione intermediate in 85% yield. The carbethoxy group was smoothly decarboxylated using trifluoroacetic acid in CH_3CN at 70°C to give the nitroindanedione **1** in 76% yield. Hydrogenation of this material using Pd/C reduced both the nitro group and the eneone double bond to give the corresponding 7-amino-3-hydroxy-indan-1-one in quantitative yield. Selective acylation of the aniline nitrogen was carried out using acetyl chloride and K_2CO_3 in acetone at 60°C. The 3-hydroxy group was eliminated using mesyl



Scheme 1. *Reagents and conditions*: (a) ethylacetoacetate, Ac_2O, Et_3N, rt, 85%; (b) TFA, CH_3CN:water, 70°C, 76%; (c) H_2, Pd/C, quant.; (d) AcCl, K_2CO_3, acetone, 60°C, 88%; (e) MsCl, Et_3N, CH_2Cl_2, reflux, 72%.

* Corresponding author.

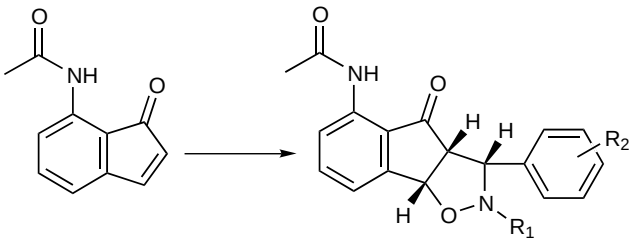
0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00517-2

chloride and triethylamine in refluxing CH_2Cl_2 to give the desired indenone system **2** in 63% overall yield.

The indenone system **2** was used in several 1,3-dipolar cyclization reactions as shown in Table 1. Typical reaction conditions were as follows: activated 3 Å molecular sieves were covered with benzene and treated with 0.2 equiv. of lanthanide catalyst. After 10 minutes the hydroxylamine[4] and aldehyde were added and allowed to form the corresponding nitrone at 50°C over 30 minutes.[5] The indenone **2** was subsequently added and the reaction stirred at rt for 18 hours. The mixture was directly purified using silica gel chromatography to give the desired cycloaddition product in good yield. Both molecular sieves and the lanthanide catalyst were required for the reaction to succeed (**3g**). Both catalysts worked equally well and gave similar *exo*/*endo* product ratios.

All compounds gave satisfactory analytical data as determined by ^{1}H NMR, MS and HPLC.[6] A complete proton assignment was performed on compound **3e**

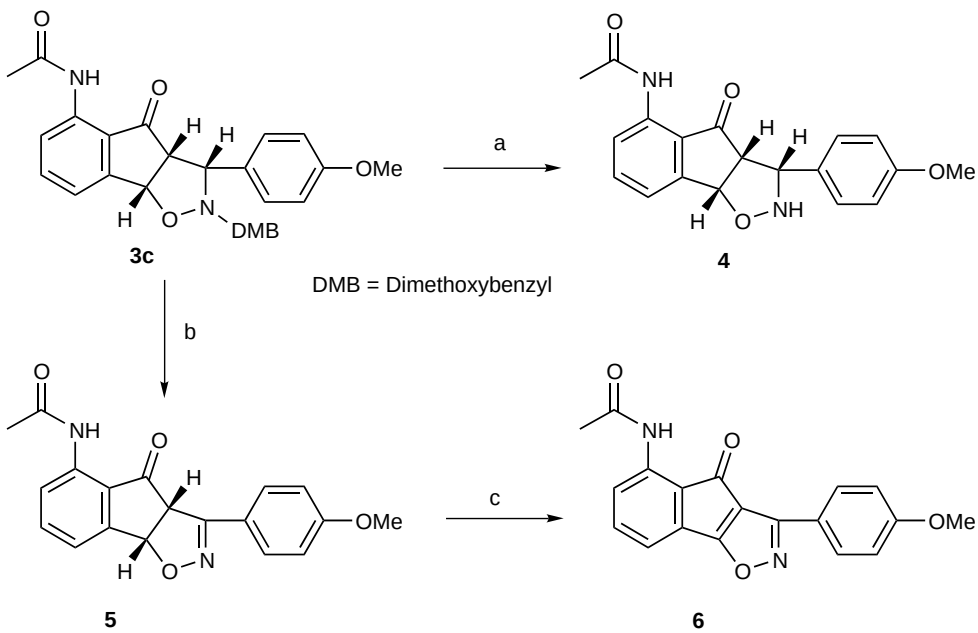
Table 1. 1,3-Dipolar cycloadditions of **2** with assorted nitrones



2 **3**

Entry	R_1	R_2	Catalyst	Yield (%)[a]	*exo*:*endo* (ratio)[b]
3a	$C_6H_5CH_2$	*p*-MeO	$Yb(OTf)_3$	88	98:2
3b	4-$MeOC_6H_4CH_2$	*p*-MeO	$Yb(OTf)_3$	84	98:2
3c	3,4-di$MeOC_6H_3CH_2$	*p*-MeO	$Yb(OTf)_3$	81	98:2
3d	3,4-di$MeOC_6H_3CH_2$	*p*-MeO	$Sc(OTf)_3$	86	98:2
3e	3,4-di$MeOC_6H_3CH_2$	*p*-NO_2	$Sc(OTf)_3$	78	98:2
3f	3,4-di$MeOC_6H_3CH_2$	H	$Sc(OTf)_3$	69	98:2
3g	3,4-di$MeOC_6H_3CH_2$	*p*-MeO	None	0[c]	

[a] Yields based on isolated and purified material.
[b] Determined by ^{1}H NMR.
[c] Both starting materials were recovered unchanged.



Scheme 2. *Reagents and conditions*: (a) TFA, CH_2Cl_2, reflux, 86%; (b) DDQ, CH_2Cl_2:water, rt, 94%; (c) 1. NBS, cat. AIBN, CCl_4, reflux, 2. KOH, MeOH, reflux, 68%.

using 2D ^{1}H NMR experiments. The preferred *exo* orientation seen in the products was determined by NOE experiments. Irradiating the C-3a proton adjacent to the indeno carbonyl induces a signal enhancement of the two protons at C-3 and C-8a. Subsequent sequential irradiation of the two protons at C-3 and C-8a causes a signal enhancement of the C-3a proton, indicating all three protons are on the same face of the indenoisoxazolidine core and confirming the *exo* product preference.

Indenoisoxazolidine **3** can be further converted to the corresponding indeonisoxazoline **5** and indenoisoxazole **6** as shown in Scheme 2. The DMB protecting group was removed by treating with TFA in refluxing CH_2Cl_2 to give the desired product **4** in 86% yield. Alternatively, the DMB group could be removed using an oxidation protocol. Treating **3c** with DDQ gave the desired indenoisoxazoline **5** in 94% yield. Attempts at further oxidizing this isoxazoline intermediate directly to the isoxazole using a variety of oxidants failed. A two-step protocol proved to work very well. Treating the isoxazoline **5** with NBS gave the desired brominated intermediate,[7] which was treated directly with KOH in MeOH at reflux to give the desired indenoisoxazole **6** in 68% yield for the two steps.

In conclusion, we have shown that lanthanide triflate-mediated 1,3-dipolar cycloadditions of nitrones with indenones is an efficient route to complex indeonisoxazolidine systems. The reaction is *exo* specific and constructs three contiguous asymmetric centers with a single reaction. In addition, these isoxazolidine intermediates can be further manipulated to give the corresponding isoxazolines or isoxazoles in good yield.

References

1. (a) Syassi, B.; El, B. B.; Benabdellah, G. A.; Hassikou, A. D.; Mohamed, N.; Riviere, M.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett*. **1999**, *40*, 7205–7209; (b) Malamidou-Xenikaki, E.; Coutouli-Argyropoulou, E. *Liebigs Ann. Chem*. **1992**, *1*, 75–78; (c) Burdisso, M.; Grunanger, P.; Rastelli, A. *J. Org. Chem*. **1990**, *55*, 3427–3429; (d) Auricchio, S.; Ricca, A. *Tetrahedron* **1987**, *43*, 3983–3986.
2. (a) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett*. **1998**, *39*, 9211–9214; (b) Sanchez-Blanco, A. I.; Gothelf, K. V.; Jorgensen, K. A. *Tetrahedron Lett*. **1997**, *38*, 7923–7926; (c) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett*. **1997**, *10*, 1039–1040; (d) Minakata, S.; Ezoe, T.; Nakamura, K.; Ryu, I.; Komastu, M. *Tetrahedron Lett*. **1998**, *39*, 5205–5208.
3. Nugiel, D. A.; Etzkorn, A. M.; Vidwans, A.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Cox, S.; Czerniak, P. M.; Doleniak, D.; Seitz, S. P. *J. Med. Chem*. **2001**, *44*, in press.
4. (a) Baldwin, J. E.; Cha, J. K.; Kruse, La. I. *Tetrahedron* **1985**, *41*, 5241–5260; (b) Dagoneau, C.; Denis, J. N.; Vallee, Y. *Synlett* **1999**, *5*, 602–604.
5. TLC showed disappearance of the starting aldehyde and hydroxylamine concurrent with the formation of the desired nitrone.
6. Analytical data for select compounds: **3a**: mp 169–171°C; ^{1}H NMR (300 MHz, $CDCl_3$) 10.0 (bs, 1H), 8.5 (d, $J=9$ Hz, 1H), 7.7 (t, $J=7.5$ Hz, 1H), 7.3 (d, $J=7.7$ Hz, 1H), 7.1 (m, 4H), 6.9 (m, 5H), 5.6 (d, $J=6.6$ Hz, 1H), 4.1 (m, 1H), 3.9 (d, $J=15$ Hz, 1H); 3.8 (s, 3H), 3.6 (s, 2H), 2.2 (s, 3H); HRMS calcd for $C_{26}H_{25}N_2O_4$ (M+H): 429.1814, found: 429.1823; **3b**: mp 173–175°C; ^{1}H NMR (300 MHz, $CDCl_3$) 10.0 (bs, 1H), 8.5 (d, $J=9$ Hz, 1H), 7.7 (t, $J=7.5$ Hz, 1H), 7.3 (d, $J=7.7$ Hz, 1H), 7.1 (m, 4H), 6.9 (d, $J=9$ Hz, 2H), 6.8 (d, $J=9$ Hz, 2H), 5.6 (d, $J=6.6$ Hz, 1H), 4.1 (m, 1H), 3.9 (d, $J=15$ Hz, 1H), 3.8 (2×s, 2×3H), 3.6 (s, 2H), 2.2 (s, 3H); HRMS calcd for $C_{27}H_{27}N_2O_5$ (M+H): 459.1920, found: 459.1925; **3c**: mp 169–170°C; ^{1}H NMR (300 MHz, $CDCl_3$) 10.0 (bs, 1H), 8.5 (d, $J=9$ Hz, 1H), 7.7 (t, $J=7.5$ Hz, 1H), 7.4 (d, $J=7.7$ Hz, 1H), 7.3 (d, $J=9$ Hz, 2H), 7.1 (m, 3H), 6.8 (d, $J=9$ Hz, 2H), 6.4 (dd, $J=9$, 2 Hz, 1H), 6.3 (d, $J=2$ Hz, 1H), 5.6 (d, $J=6.6$ Hz, 1H), 4.1 (m, 2H), 3.8 (2×s, 2×3H), 3.6 (s, 3H), 2.2 (s, 3H); HRMS calcd for $C_{28}H_{29}N_2O_6$ (M+H): 489.2026, found: 489.2010; **3e**: mp 165–167°C; ^{1}H NMR (600 MHz, $CDCl_3$) 9.9 (bs, 1H), 8.5 (d, $J=8.2$ Hz, 1H), 8.1 (d, $J=8.8$ Hz, 2H), 7.7 (t, $J=7.9$ Hz, 1H), 7.4 (d, $J=7.5$ Hz, 1H), 7.3 (d, $J=8.8$ Hz, 2H), 7.1 (d, $J=8.4$ Hz, 1H), 6.4 (dd, $J=8.4$, 2.4 Hz, 1H), 6.3 (d, $J=2.4$ Hz, 1H), 5.6 (d, $J=6.4$ Hz, 1H), 4.2 (d, $J=9.2$ Hz, 1H), 3.9 (s, 2H), 3.8 (s, 3H), 3.7 (dd, $J=9.2$, 6.4 Hz, 1H), 3.6 (s, 3H), 2.1 (s, 3H); HRMS calcd for $C_{27}H_{26}N_3O_7$ (M+H): 504.1771, found: 504.1782; **6**: mp 210–212°C; ^{1}H NMR (300 MHz, $CDCl_3$) 9.9 (bs, 1H), 8.6 (d, $J=9$ Hz, 1H), 8.1 (d, $J=9$ Hz, 2H), 7.4 (t, $J=7.5$ Hz, 1H), 7.1 (d, $J=9$ Hz, 1H), 7.0 (d, $J=9$ Hz, 2H), 3.9 (s, 3H), 2.3 (s, 3H); HRMS calcd for $C_{19}H_{15}N_2O_4$ (M+H): 335.1032, found: 335.1022.
7. Bromination occurs exclusively on C-3a adjacent to the indenone carbonyl. ^{1}H NMR indicates the process was stereospecific as only one brominated intermediate was observed.