Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5679-5682, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01204-X

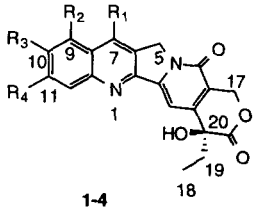
Novel Syntheses of Camptothecin Alkaloids, Part I. Intramolecular [4+2] Cycloadditions of N-Arylimidates and 4H-3,1-benzoxazin-4-ones as 2-Aza-1,3-Dienes

Joseph M.D. Fortunak,* Antonietta R. Mastrocola, Mark Mellinger, Nicolas J. Sisti, Jeffery L. Wood and Zhi-Ping Zhuang

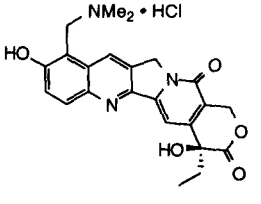
Chemical Process R&D, DuPont Merck Pharmaceutical Co.,
Chambers Works, PRF(S1) Deepwater, NJ 08023-0999

Department of Synthetic Chemistry, SmithKline Beecham Corporation,
709 Swedeland Road, King of Prussia, PA 19406-0939

Abstract: The first reported intramolecular [4+2] cycloadditions of both N-arylimidates and 4**H**-3,1-benzoxazin-4-ones acting as 2-aza-1,3-dienes are described. Reaction with unactivated alkynes leads to pyrrolo[3,4-b]quinolines which constitute the ABC ring system of camptothecins. Copyright © 1996 Elsevier Science Ltd



1-4

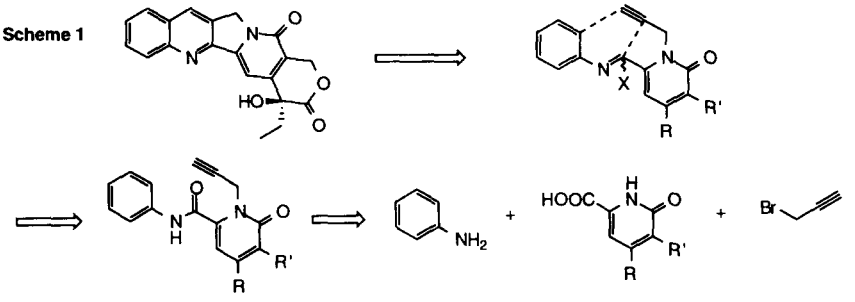


5

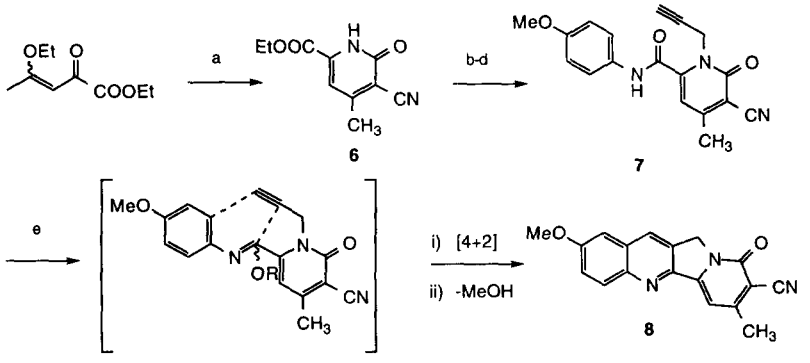
1	R_1 - R_4 = H	Camptothecin
2	R_1 = C_2H_5, R_3 = OCO-(4-piperidinyl piperidine)	Irinotecan(Daiichi/Yakult)
3	R_3-R_4 = ethylenedioxy R_1 = CH_2(N-Me-piperazine)	GI-147211C(Glaxo)
4	R_2 = NH_2	9-aminocamptothecin(NCI)
5	as shown	Topotecan(SmithKline Beecham)

Camptothecin[1] is a selective inhibitor of mammalian topoisomerase I[2,3] originally isolated from the Chinese tree *Camptotheca acuminata*. A number of camptothecin analogues (**2-5**) are being developed as anticancer agents.[4,5] Several intriguing total syntheses of camptothecin have been published[6] of which perhaps the most commercially viable originate from the Comins group.[7] With the recent FDA marketing approval of topotecan (**5**)[4a] we wish to report some of our efforts from the SmithKline Beecham process chemistry group in this area. Scheme 1 indicates our retrosynthetic strategy used to synthesize camptothecin and various of its analogues, including topotecan. We assembled the pyrrolo[3,4-b]quinoline ring system (ABC rings) of camptothecins by the previously unknown, intramolecular [4+2] cycloaddition of unactivated alkynes with either N-arylimidates or 4**H**-3,1-benzoxazin-4-ones (Schemes 2 and 3). ABCD ring precursors of camptothecins were therefore prepared from the appropriate aniline, a propargyl unit, and various 2-pyridone-6-carboxylic acids.

Scheme 1



Scheme 2 illustrates our initial success. The 2-(1**H**)-pyridone **6**[6a] was converted in three steps to **7** in 51% overall yield. Stirring of **7** with three equivalents of trimethyloxonium fluoroborate in methylene chloride solution at 20 °C gave the corresponding O-methylimidate (4:1 mixture of stereoisomers, major isomer not determined) indicated by ^{1}H NMR spectroscopy. The desired, intramolecular [4+2] cycloaddition and subsequent elimination of methanol did occur, albeit slowly, under these conditions. Replacement of the solvent with acetonitrile and refluxing for six hours gave a single major product (analytical TLC/HPLC). The product was isolated by concentration of the solvent and crystallization from hot methanol to give the tetracyclic quinoline **8** in 82% yield from **7**.[8] This amounts to a formal total synthesis of (±) 10-methoxycamptothecin.[6b,c]

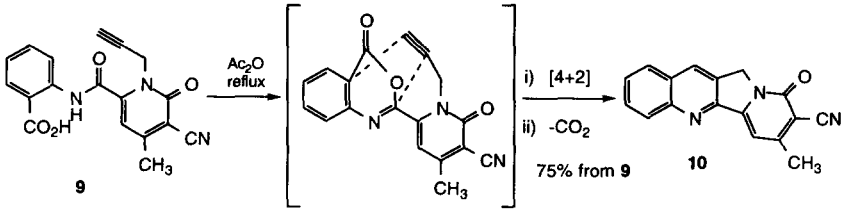


Scheme 2 Reagents and Conditions: a) cyanoacetamide, K_2CO_3, acetone, reflux; 82% b) propargyl bromide, DMF, K_2CO_3 ; 65% c) NaOH, aq. DMF; 95% d) *p*-anisidine, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide:HOBT, CH_2Cl_2; 83% e) CH_2Cl_2, Me_3OBF_4, RT °; followed by CH_3CN, reflux; 82%

The formation of **8** is effectively the intramolecular [4+2] cycloaddition of an "electron-neutral" alkyne with a 2-aza-1,3-diene, with the aryl ring serving as a 2π component of the diene. Although the intramolecular cycloaddition of 2-azadienes has been reported[9] and, in special circumstances, N-arylimines and N-arylimmonium salts have been condensed in a [4+2] fashion with electron-rich olefins[10-12] we believe this to be the first report of N-arylimidates serving as 4π components in a Diels-Alder reaction.[13]

In some cases cycloaddition through the intermediate imidate gave poor yields. This was dependent upon the substitution pattern on the aromatic ring and the stability of the imidate towards competitive rearrangement[13] and/or decomposition. Substrates with at least one electron-donating substituent (*e.g.*, methoxy) on the aromatic ring gave good yields of product. When yields are poor, a preferred alternative is cycloaddition through the analogous 4**H**-3,1-benzoxazin-4-one.[14] Benzoxazinone **9** in Scheme 3 was derived from **6** by ester hydrolysis followed by coupling with anthranilic acid (CDI in THF, 88% yield after recrystallization). Ring closure to form the benzoxazinone in refluxing acetic anhydride[15] also resulted in intramolecular cycloaddition and loss of carbon dioxide to give the corresponding quinoline. Tetracycle **10** was

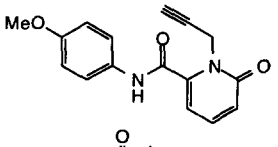
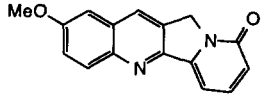
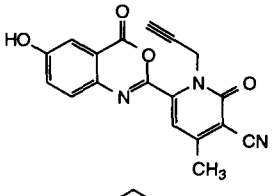
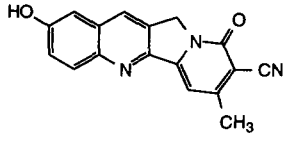
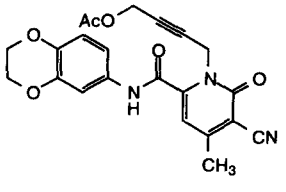
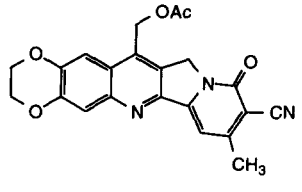
obtained in 75% yield (*cf.* Scheme 3) from **9** in this manner. The conversion of **10** to racemic camptothecin is known.[6b,c] The only analogous reaction of benzoxazinones is their stepwise [4+2] addition with ynamines, giving rise to quinolines with narrowly restricted substitution patterns.[16]



Scheme 3

We have not extensively examined the reactions of N-arylimidates or 4**H**-3,1-benzoxazin-4-ones with a range of dienophiles. A few additional intramolecular cycloadditions are listed in the Table below. Our current results are consistent with the products being formed through a [4+2] cycloaddition, although the possibility of either reaction occurring through a stepwise mechanism has not been rigorously disproven. We have used this strategy to carry out total syntheses of compounds **1-3** and **5**. A concise total synthesis of camptothecin analogues, including (S)-topotecan (**5**) is described in the communication immediately following.[17]

TABLE

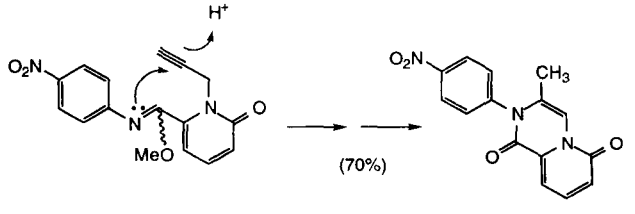
Substrate	Method (yield)	Product
	A (65%)	
	B (74%)	
	A (48%)	

Method A : 3 eq. trimethyloxonium tetrafluoroborate; acetonitrile, 20 °C followed by reflux
Method B : reflux in acetic anhydride

References and Notes

1. Wall, M.E.; Wani, M.C.; Cook, C.E.; Palmer, K.H.; McPhail, A.T.; Sim, G.A. *J.Am. Chem. Soc.* **1966**, *88*, 3888.
2. Hsiang, Y.-H.; Hertzberg, R.; Hecht, S.; Liu, L.F. *J. Biol. Chem.* **1985**, *260*, 14873.
3. Giovanella, B.C.; Stehlin, J.S.; Wall, M.E.; Wani, M.C.; Nicholas, A.W.; Liu, L.F.; Silber, R. Potmesil, M. *Science* **1989**, *246*, 1046.

4. a) Kingsbury, W.D.; *et. al. J. Med. Chem.* **1991**, *34*, 98.
   b) Sawada, S.; *et. al. Chem. Pharm. Bull.* **1991**, *39*, 1446.
   c) Miyasaka, T.; Sawada, S.; Nokata, K.; Mutai, M. *U.S. Patent* 4 545 880, **1985**.
   d) Luzzio, M.J.; *et. al. Proc. Am Assoc. Cancer Res.* **1993**, *34*, 332..
5. Irinotecan (**2**) is a marketed anticancer agent in Japan and is currently in Clinical development in the United States sponsored by the Upjohn/Pharmacia Corp.
6. a) Wani, M.C.; *et. al. J. Med. Chem.* **1980**, *23*, 554.
   b) Eckert, H. *Angew. Chem. Int'l. Ed. Engl.* **1981**, *20*, 208.
   c) Pan, P.C.; *et. al. Acta Chim. Sinica* **1975**, *33*, 71.
   d) Cia, J.C.; Hutchinson, C.R. *Chem. Heterocycl. Compd.* **1983**, 25, 753.
   e) Cia, J.C.; Hutchinson, C.R. *The Alkaloids: Chemistry and Pharmacology*, Brossi, A., Ed.; Academic Press: New York, **1983**; Vol. 21, p. 101.
   f) Shen, W.; Coburn, C.A.; Bornmann, W.G.; Danishefsky, S.J. *J. Org. Chem.* **1993**, *58*, 611.
   g) Curran, D.P.; Bo, S.-B.; Josien, H. *Angew. Chem. Int'l. Ed. Engl.* **1995**, *54*, 2683; Curran, D.P.; Liu, H. *J. Am. Chem. Soc.*, **1992**, *114*, 5863; Curran, D.P.; Ko, S.-B. *J. Org. Chem.*, **1994**, *59*, 6139.
   h) Jew, S.-s.; Ok, K.-d.; Kim, H.-j.; Kim, M.G.; Kim, J.M.; Hah, J.M.; Cho, Y.-s. *Tetrahedron: Asymmetry* **1995**, *6*, 1245.
   i) Fang, F.G.; Xie, S.; Lowery, M.W. *J. Org. Chem.*, **1994**, *59*, 6142.
7. a) Comins, D.L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35* 5331.
   b) Comins, D.L.; Hong, H.; Saha, J.K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120.
   c) Comins, D.L.; Saha, J.K. *Tetrahedron Lett.* **1995**, *36*, 7995.
   d) Comins, D.L.; Baevsky, M.F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.
8. Compounds were identified by ^{1}H NMR, IR and Mass spectral analysis. Purity was determined by HPLC. New compounds were additionally characterized by ^{13}C NMR, exact mass determination and/or elemental analysis. Yields are given after purification.
9. Barluenga, J.; *et. al. Synlett.* **1990**, 129.
10. Grieco, P.A.; Bahsas, A.; *Tetrahedron Lett.* **1988**, *29*, 5855.
11. Mellor, J.M.; Merriman, G.D.; Mitchell, P.L.; *Tetrahedron* **1995**, *51*, 12383.
12. For a review of applicable references see Boger, D.L.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Wasserman, H., Ed.; Academic Press: San Diego, **1987**; Vol. 47, pp. 255-260, 278-299.
13. Since formation of the imidate produces one mole equivalent of fluoroboric acid this reaction is likely an inverse electron-demand [4+2] cycloaddition of the protonated azadiene with the "electron-rich" alkyne. The reaction occurs, although more slowly, through the neutral imidate. Photolysis, radical traps or initiators have no significant effect on the reaction. The benzoxazinones react uniformly in a [4+2] fashion whereas the p-nitro-N-arylimidate reacts as below, giving the desired cycloaddition in poor yield (15-20%; compare with ref. 10). Lewis acid catalyzed reaction of various imidates or reaction through the O-silyl-imidates also gives primarily the reaction pathway indicated below.



14. Heller, G.; Fiesselman, G. *Justus Liebig's Ann. Chem.* **1902**, *324*, 134.
15. Fenton, G.; Newton, C.G.; *et. al. J. Med. Chem.* **1989**, *32*, 265.
16. a) Hofle, G.; Hollitzer, O.; Steglich, W. *Angew. Chem. Int'l. Ed. Engl.* **1972**, *11*, 720.
    b) Steglich, W.; Hollitzer, O. *Angew. Chem. Int'l. Ed. Engl.* **1973**, *12*, 495.
17. A preliminary, partial disclosure of this work was first presented at the University of New Orleans, February 21, 1992.

(*Received in USA* 12 *April* 1996; *revised* 11 *June* 1996; *accepted* 12 *June* 1996)