Pergamon

Tetrahedron Letters 43 (2002) 1645–1648

TETRAHEDRON LETTERS

Construction of *cis*-azadecalone units via novel intermolecular Diels–Alder reaction

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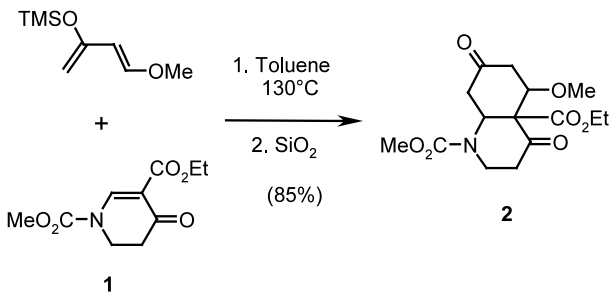
Received 13 November 2001; revised 7 January 2002; accepted 8 January 2002

Abstract—*N*-Methoxycarbonyl-5-ethoxycarbonyl-2,3-dihydropyridin-4-one **1** reacts under thermal or Lewis acid-catalysed conditions with trimethylsilyloxybutadienes to give *cis*-azadecalones via a formal [4+2] cycloaddition.

Alkaloids containing the 1-azadecalin moiety are abundant in nature and many exhibit significant biological activities.[1] Our interest in the development of new strategies for the synthesis of such units prompted us to consider a new approach relying on Diels–Alder reaction of *N*-methoxycarbonyl-2,3-dihydropyridin-4-ones as dienophiles. To the best of our knowledge, there is no reported example of such intermolecular cycloadditions.[2] Herein, we report our results concerning the implementation of this strategy to access highly functionalised octahydroquinoline skeletons.

Preliminary attempts showed that *N*-methoxycarbonyl-2,3-dihydropyridin-4-one was inert as the dienophile,[3] under various conditions. Therefore, we decided to explore the behaviour of a dihydropyridone bearing at C5 an alkoxycarbonyl substituent, that was expected to enhance the reactivity of the enamine moiety as a dienophile.[4]

Substrate **1**, readily prepared from the commercially available 3-ethoxycarbonyl-piperid-4-one hydrochloride,[5] was first reacted under thermal conditions, with Danishefsky's diene in toluene, at 130°C (sealed tube), overnight. After purification on silica gel, desilylated adduct **2** was isolated as a 80/20 diastereomeric mixture (vide infra) in 85% overall yield (Scheme 1). However,



Scheme 1.

heating compound **1** in the presence of less electron rich dienes (isoprene, 2,3-dimethyl-1,3-butadiene, furan, 2-trimethylsilyloxyfuran, 1- and 2-trimethylsilyloxy-1,3-butadienes) did not yield any cycloadduct, even after 5 days of reaction.

We next examined the Lewis acid catalysed version of these cycloadditions. The use of BF_3–OEt_2, $TiCl_4$, TMSOTf and Et_2AlCl did not give any satisfactory result. Isoprene and 2,3-dimethylbutadiene were shown to be unreactive, whereas trimethylsilyloxy-butadienes polymerised in most cases. However, 1,4-addition compounds **3** and **4** (Fig. 1) were isolated following reaction of **1** with furan and 2-trimethylsilyloxyfuran, respectively (27–78% yields),[6] as previously reported in the case of some enones.[7]

We then turned our attention towards Lewis acids derived from scandium ($Sc(OTf)_3$),[8] copper

Keywords: dihydropyridone; cyclocondensation; stereoselective; Lewis acid; octahydroquinoline.

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PII: S0040-4039(02)00068-0

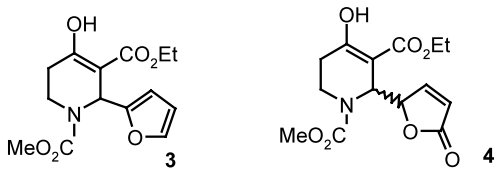


Figure 1.

($Cu(OTf)_3$),[9] bismuth ($BiCl_3$ and $Bi(OTf)_3$)[10] and ytterbium ($Yb(OTf)_3$).[11] Under these conditions, unactivated dienes led to similar failures to those reported above. In contrast, trimethylsilyloxybutadienes afforded, in most cases, the corresponding cycloadducts (Table 1).

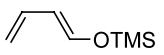
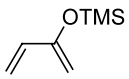
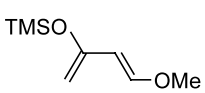
With the exception of $BiCl_3$ which was totally inefficient (entry 3), reaction of **1** in the presence of these Lewis acids with 1-trimethylsilyloxy-1,3-butadiene afforded the expected cycloadducts **5a** and/or **5b**, along with the monocyclic enal **6** (Scheme 2). The diastereoselectivity of **5** was highly dependant on the nature of the Lewis acid employed (entries 1–5). The best chemical yield in cycloadduct (**5a** and **5b**) was obtained with $Yb(OTf)_3$, as the catalyst in refluxing CH_2Cl_2, for 24 h (entry 5). Noteworthy in the latter case was the observation that a prolonged reaction time above 48 h resulted in the obtention of only one diastereomer **5a** (entry 6).

Formation of enal **6** is believed to result from the protodesilylation of the Mukaiyama's retroaldolisation product of cycloadducts **5**. Indeed, when submitted to an overnight reflux in CH_2Cl_2 in the presence of $Yb(OTf)_3$, a purified diastereomeric mixture of **5a** and **5b** (30:70) mainly yielded enal **6** (38%) along with a trace of **5a** (7%) and substrate **1** (10%). Moreover, when the same experiment was conducted in the presence of an excess of the diene, **5a** was isolated as the major product (68%), along with **6** (7%) and **1** (4%). These results suggested an isomerisation of the kinetic diastereoisomer **5b** into the thermodynamic one **5a** either by successive retro-Mukaiyama/Mukaiyama reactions (via the silylated enol of **6**) or retro Diels–Alder/Diels–Alder reactions. The formation of **1** stemmed either from retro-Mukaiayama/retro-Michael or from retro-Diels–Alder processes. Moreover, in order to ascertain the relative stereochemistry of the thermodynamic isomer **5a**, the latter was transformed in two steps into the corresponding crystalline benzoate **7a** (Scheme 2), the configuration of which was secured by X-ray analysis.[12]

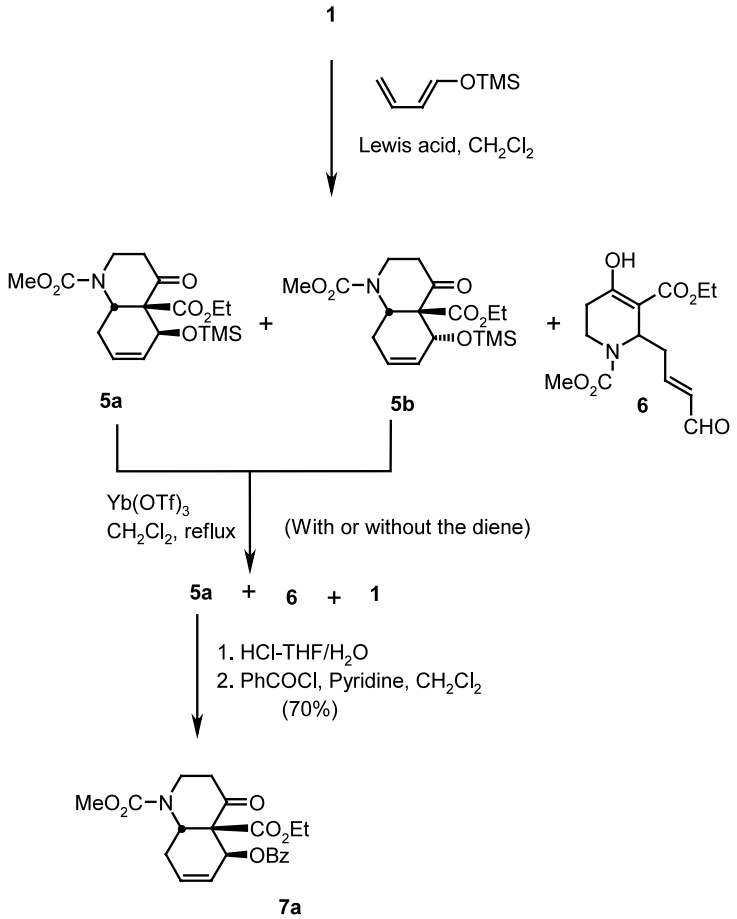
2-Trimethylsilyloxy-1,3-butadiene was then reacted with dienophile **1** in the presence of various Lewis acids, among which only $Sc(OTf)_3$, $Cu(OTf)_2$ and $Yb(OTf)_3$ efficiently catalysed the expected cycloaddition (entries 7, 8 and 11). In all cases, azadecalone **8** was isolated (after acidic treatment) as a single stereomer. Once again, the *cis*-configuration of this compound was assigned based on X-ray data[12] (Scheme 3).

As far as Danishefsy's diene was concerned, the only interesting results were obtained with $BiCl_3$ and $Yb(OTf)_3$. In the former case (entry 14), three compounds were identified in the crude mixture: desilylated cycloadduct **2**, enone **9** (resulting from **2** after elimination of methanol), along with a trace of phenol **10** (Scheme 3). Compound **2** was isolated as a mixture of two diastereomers, in a ratio different from the one obtained above. Attempts to isolate enone **9** by silica gel chromatography mainly resulted in the obtention of phenol **10**, through retro-Michael and subsequent retro-

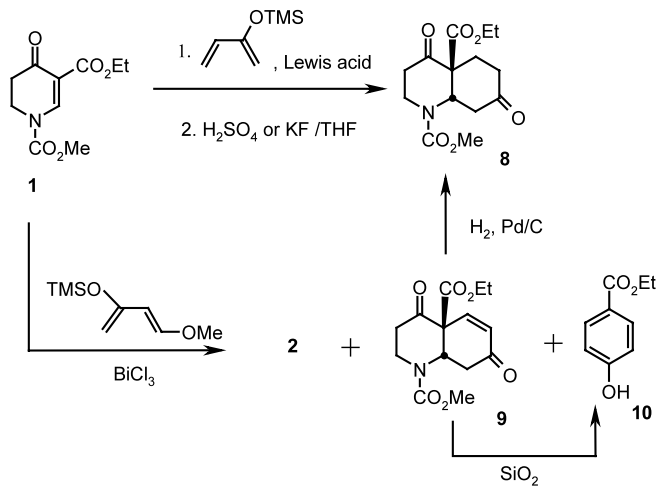
Table 1.

Entry	Diene	Lewis acid (equiv.)	Temp. (time)	Products (yield)[a]
1		$Sc(OTf)_3$ (0.05)	−78 to 0°C (5 h)	**5a**+**5b** (44%) [86:14][b] **6** (34%)
2		$Cu(TOf)_3$ (0.1)	rt (4 h)	**5a**+**5b** (35%) [57:43][b] **6** (7%)
3		$BiCl_3$ (0.1)	rt	–[c]
4		$Bi(OTf)_3$ (0.1)	rt (5 h)	**5a** (46%) **6** (32%)
5		$Y(OTf)_3$ (0.05)	Reflux (24 h)	**5a**+**5b** (78%) [55:45][b] **6** (7%)
6		$Y(OTf)_3$ (0.05)	Reflux (48 h)	**5a** (64%) **6** (16%)
7		$Sc(OTf)_3$ (0.05)	−78°C to rt (5 h)	**8** (56%)
8		$Cu(TOf)_3$ (0.1)	rt (24 h)	**8** (56%)
9		$BiCl_3$ (0.1)	rt	–[c]
10		$Bi(OTf)_3$ (0.1)	rt	–[c]
11		$Y(OTf)_3$ (0.05)	Reflux (20 h)	**8** (64%)
12		$Sc(OTf)_3$ (0.05)	rt	–[c]
13		$Cu(TOf)_3$ (0.1)	0°C (4 h)	–[d]
14		$BiCl_3$ (0.1)	rt (12 h)[e]	**2** (26%) **8** (50%) **10**(15%)
15		$Bi(OTf)_3$ (0.1)	rt	–[c]
16		$Y(OTf)_3$ (0.05)	rt (15 min)[e]	**8** (56%) **10** (18%)

[a] Isolated yields.
[b] Diastereomeric ratio as estimated by ^1H NMR and GC.
[c] No reaction was observed.
[d] Unreacted starting material was recovered. Only trace of 4-hydroxyacetophenone resulting from the dimerisation of the diene was isolated.
[e] Products isolated after submission of the crude reaction mixture to catalytic hydrogenation.



Scheme 2.



Scheme 3.

Claisen type reactions followed by aromatisation. Formation of phenol **10** has already been reported in the case of oxo-analogues.[2] To prevent this degradation, the crude reaction mixture was subjected to catalytic hydrogenation prior to purification. This enable us to isolate compounds **2**, **10** and a ketone, whose spectroscopic data were in full agreement with compound **8**, previously obtained from 2-trimethylsilyloxy-1,3-butadiene (Table 1). This result led us to attribute a *cis* junction to both diastereomers of **2**, these isomers being epimers at the stereogenic centre bearing the methoxy group.

Finally, a very fast reaction was observed in the presence of $Yb(OTf)_3$ as the catalyst, mainly yielding ketone **8** and phenol **10** after hydrogenation (entry 16). Of note was the absence of methoxylated derivative **2** in the reaction mixture.

In these preliminary studies, we have established the feasibility of intermolecular Diels–Alder cyclocondensations between *N*-methoxycarbonyl-2,3-dihydropyridin-4-one and trimethylsilyloxybutadienes which allows the construction of highly functionalised *cis*-fused azadecalones, a frequent central core of a variety of alkaloids.[13] Further work aimed at exploiting the synthetic potentialities of this methodology is currently underway.

References

1. (a) Daly, J.; Garraffo, M.; Spande, T. In *Alkaloids*: *Chemical and Biochemical Perspectives*; Pelletier, S. W., Ed. Alkaloids from amphibian skins; Pergamon, 1999; Vol. 13, pp. 1–161; (b) Blumenkopf, T. A.; Heathcock, C. H. In *Alkaloids*: *Chemical and Biochemical Perspective*; Pelletier, S. W., Ed. Synthesis of Lycopodium alkaloids; Wiley: New York, 1985; Vol. 3, pp. 185–240.
2. While we were engaged in this study, a similar approach was described with dihydropyrones as dienophiles: Chen, D.; Wang, J.; Totah, N. *J. Org. Chem.* **1999**, *64*, 1776–1777.
3. A similar absence of reactivity has been previously reported in a related case. See reference 15 in: Wenkert, E.; Moeller, P.; Piettre, S. *J. Am. Chem. Soc.* **1988**, *110*, 7188–7194.
4. Moreover, this added functionality would allow the introduction of a chiral auxiliary.[5]
5. For the preparation of compound **1** and its chiral menthyl derivatives which have previously been examined as Michael acceptors, see: Brocherieux-Lanoy, S.; Dhimane, H.; Vanucci-Bacqué, C.; Lhommet, G. *Synlett* **1999**, *4*, 405–408.
6. Compound **4** was isolated as 1/1 mixture of diastereomers.
7. Similar results were reported previously for furan: (a) Liu, H.; Ulibarri, G.; Browne, E. *Can. J. Chem.* **1992**, *70*, 1545–1554; (b) Satake, Y; Tadano, K. *J. Carbohydr. Chem.* **1997**, *16*, 441–447. For 2-trimethylsilyloxyfuran: (c) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015–17028.
8. Kobayashi, S. *Synlett* **1994**, 689–701.
9. Brunel, J. M.; Del Campo, B.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 9663–9666.
10. Garrigues, B.; Gonzaga, F.; Robert, H.; Dubac, J. *J. Org. Chem.* **1997**, *62*, 4880–4882.
11. Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *24*, 721–724.
12. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 173235 (**7a**) and CCDC 173236 (**8**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
13. Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583–4592.