Published in final edited form as:

Tetrahedron Lett. 2011 August 3; 52(31): 3957–3959. doi:10.1016/j.tetlet.2011.05.110.

Further Expansion of the *trans*-Diels-Alder Paradigm: Reductive Alkylation of α -Cyanoketones

Feng Peng[†], Robin E. Grote[†], and Samuel J. Danishefsky^{†,‡}

[†] Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, NY 10027

[‡] Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10065

Abstract

Reductive alkylation of Diels-Alder derived ring junction- α -cyanoketones provides a route to *trans*-fused bicyclic systems.

Keywords

Diels-Alder; Reductive Alkylation; *trans*-Octalone; Cyanoketone

In the context of our “pattern recognition” approach as an aid in retrosynthetic analysis, we seek to discern substructural units – or motifs – within the target structures that are accessible through reasonable chemistry.¹ Translating a target synthesis problem to the identification of such an accessible pattern (or patterns) may well be non-obvious but may, in the end, provide a particularly clear path for progress. Obviously, the value of this type of thought process grows as the number of accessible patterns (“safe havens”) increases. For example, recognition of a *cis*-fused junction in a bicyclic motif where at least one of the rings is 6-membered, typically suggests a classical Diels-Alder (DA)-based strategy. In an effort to expand the menu of useful patterns available, we recently undertook to study a possible *trans*-DA paradigm.² The logic involves equipping a cyclic dienophile with a temporary activating group which enhances proclivities for formation of the bicyclic adduct. Subsequent cleavage of this angular functionality and introduction of a new function at the same site, with overall *inversion* of configuration provides entry into the *trans*-fused series (Figure 1a).^{2a} In pursuit of such a “*trans*-DA” paradigm, we have developed the capacity to rapidly construct *trans*-fused decalinoid motifs bearing angular methyl groups (Figure 1b).^{2c} Thus, following DA cycloaddition, *cis*-fused α -bromoketones (**1**) are obtained. Exposure to lithium naphthalide (LN), and alkylation of the resultant enolate **2** with iodomethyl phenyl sulfide provides the angularly functionalized *trans*-fused adduct with high *trans* stereoselectivity in the very important octalin series (**3**). Following Raney Ni-mediated desulfurization, the angularly methylated *trans*-octalone system is in hand. While direct methylation also provides preferential *trans*-fused stereoisomer in the octalin series, the two-step protocol described above affords significantly higher *trans*-selectivities.

Based on precedent from our α -bromoketone-based studies we hypothesized that it should also be possible to functionalize an analogous system bearing an angular *cyano* moiety (Figure 1c). It seemed likely that an α -cyanocyclenone system (cf. **4**) would be a more reactive dienophile than is its corresponding α -bromo counterpart.

Indeed, Liu and co-workers had reported that angularly cyanylated systems of the type **4** could be prepared by DA cycloaddition. Interestingly, they had reported that methylation of these compounds gave *cis*-fused products. However, the systems employed in their studies incorporated structural features which would be expected to dispose them toward *cis*-alkylation.^{3,4} Thus, we sought to explore the feasibility of converting *cis*-fused α -cyanoketones (**4**) to *trans*-fused angularly alkylated products through recourse to the conditions which were successful in the α -bromoketone alkylation (see Figure 1b). In this context, we could also explore a tangential, nonetheless interesting, question, i.e. whether the distereoselectivities of enolate alkylations would be essentially the same starting with a α -bromo or α -cyano precursors.

We first examined the direct methylation of α -cyanoketones. Thus, a variety of *cis*-fused cycloadducts (**4a–4d**) readily underwent angular alkylation with MeI as an electrophile (Method A). As anticipated, *trans*-fused adducts were predominantly formed, albeit with moderate levels of selectivity (Table 1). The isolated *cis*- and *trans*- isomers were rigorously characterized through spectral comparison with known standards prepared by alternative methods.^{2c}

Having established the propensity of the enolate derived from the α -cyanoketone to undergo alkylation to provide *trans*-fused adducts, we next sought to improve the selectivity ratios of the products (Table 1). As precedented,^{2c} when iodomethyl phenyl sulfide⁵ was used as the electrophile, the product stereoselectivities were markedly improved. The levels of alkylation selectivity achieved under these conditions were quite similar to those observed in our previous study using α -bromoketone substrates. However, we note that, in general, the analogous α -bromoketones appear to afford somewhat higher *trans*:*cis* ratios.⁵

Finally, we examined the reductive allylation of α -cyanoketones **4b** and **4c**, with allylbromide as the electrophile. The reactions were conducted under conditions that were previously reported to provide exclusively *cis*-fused products.³ Interestingly, we also obtained predominantly *cis*-fused adducts, though in our hands, isomeric mixtures (2:1 and 3:1, respectively) were observed (Scheme 1).

In summary, we describe herein a useful extension of our *trans*-Diels-Alder paradigm, through the development of a *trans*-selective reductive alkylation of *cis*-fused α -cyanoketone Diels-Alder adducts. We note that our stereochemical assignments are fully supported by comparisons with known standards in the readily accessible (via Diels-Alder reactions) *cis* series. Moreover, the selectivities reported herein are entirely consistent with those obtained in the context of our analogous α -bromoketone alkylation protocol. The method described here has the major advantage in that it exploits the cyano substituted dienophile which is much more reactive than is the previously used bromo version. Experiments building upon these findings are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIH (HL25848 to S.J.D.). F.P. thanks Eli Lilly and Company for a graduate fellowship. Special thanks to Ms. Rebecca Wilson for valuable help in editing the manuscript.

References

1. Wilson RM, Danishefsky SJ. *J Org Chem.* 2007; 72:4293–4305. [PubMed: 17539594]
2. (a) Kim WH, Lee JH, Danishefsky SJ. *J Am Chem Soc.* 2009; 131:12576–12578. [PubMed: 19685875] (b) Kim WH, Lee JH, Aussedat B, Danishefsky SJ. *Tetrahedron.* 2010; 66:6391–6398. [PubMed: 20717474] (c) Lee JH, Zhang Y, Danishefsky SJ. *J Am Chem Soc.* 2010; 132:14330–14333. [PubMed: 20863105] (d) Shibatomi K, Futatsugi K, Kobayashi F, Iwasa S, Yamamoto H. *J Am Chem Soc.* 2010; 132:5625–5627. [PubMed: 20373752]
3. Zhu J, Shia K, Liu H. *Chem Comm.* 2000:1599–1600.
4. (a) Liu HJ, Yip J, Shia KS. *Tetrahedron Lett.* 1997; 38:2253–2256. (b) Liu HJ, Zhu JL, Shia KS. *Tetrahedron Lett.* 1998; 39:4183–4186. In some instances, Liu and coworkers reported very high levels of cis selectivity. However, these were in cases bearing a methyl group para to the ketone. We, too, have found this trend.
5. (a) Trost BM, Kunz RA. *J Org Chem.* 1974; 39:2648–2650. (b) Trost BM, King SA. *J Am Chem Soc.* 1990; 112:408–422.

Figure 1.

Scheme 1. Alkylation of α -cyanoketones **4a** and **4b**.

Table 1

α -cyanoketones.^a

	Method A	Method B
	product	product
	yield <i>trans:cis</i>	yield <i>trans:cis</i>
α -cyanoketone	<p>4a</p>	<p>6a</p>
	78% 7:1	72% 7:1

<i>α</i> -cyanoketone	Method A		Method B	
	product	yield <i>trans:cis</i>	product	yield <i>trans:cis</i>
4b	5	4	6b	6
	(i) LN, THF (ii) HMPA (iii) MeI Method A		(i) LN, THF (ii) HMPA (iii) PhSCH ₂ I Method B

α -cyanoketone	Method A		Method B	
	product	yield <i>trans:cis</i>	product	yield <i>trans:cis</i>
		75% 3:1		67% 7:1
		67% 2:1		62% 7:1