A Novel Sequential Aminodiene Diels–Alder Strategy for the Rapid Construction of Substituted Analogues of Kornfeld’s Ketone

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Received September 13, 2002

ABSTRACT

Through a novel sequence of aminodiene Diels–Alder reactions, amidofurans 18a-c were converted to tricyclic ketones 21a-c in moderate to good yields. Ketone 21a could be converted to Uhlé’s ketone (6) by cleaving the tert-butyl carbamate and oxidatively removing the methyl ester. Tricycle 21a readily underwent bromination to give 22. Formation of the corresponding enol triflate 25 followed by carbonylation gave ester 27, which was then coupled with N-methyl propiolamide to furnish 26.

Indole alkaloids constitute a major family of natural products whose structural diversity and broad pharmacological activity have made them both synthetically interesting and medically important.¹ The ergot alkaloids, of which lysergic acid (1) is representative, are particularly important as they possess the widest spectrum of biological activity found in any family of natural products.² Small variations in the substituents present on the core tetracycle change the biological response from psychotropic (LSD, 2) to oxytocic (ergonovine, 3). Several synthetic derivatives are used clinically as antimigrain (lisuride), analgesic (mertgoline, 4), and anti-Parkinsonian (pergolide, 5) therapeutics, to name just a few.³

The clinical success of these synthetic derivatives has prompted keen interest in indoles that are substituted around the aryl A ring. For example, compounds with the general structure 8 have antihypertensive, antiparkinson, and prolactin-inhibiting activities,⁴ while compounds represented by 9 are analgesic and cell protective agents.⁵ The position of the tert-butyl group (R) in indole 10 strongly impacts on the selectivity of these molecules for 5-HT₁A vs 5-HT₂ receptors.⁶

Many of the synthetic studies dealing with ergot structures focus on Uhlé’s (6)⁷,⁸ and Kornfeld’s (7)⁹–¹¹ ketones, and methodologies that efficiently construct these tricycles have been important tools for medicinal chemists. Consequently,

¹ NIH postdoctoral Fellow; grant GM20666.
much attention has been centered on synthetic methods that construct indoles, particularly 3,4-disubstituted indoles. New procedures that can selectively generate polysubstituted indoles and also allow for the rapid construction of substituted analogues such as 6 or 7 would be of particular use to the medicinal community.

As part of our ongoing program dealing with the intramolecular Diels–Alder reaction of 2-amidofurans, we had previously noted that polysubstituted dihydroindoles could easily be prepared. It occurred to us that the strategic use of some aminodiene chemistry recently developed by Rawal was imagined, consequently, the key amidofuran was imagined to come about from a ring opening and dehydration of an oxabicycle tethered such that it would be of particular use to the medicinal community. In turn, this oxabicycle is the result of an intramolecular Diels–Alder reaction of amidofuran 13 with a cyclohexenone moiety tethered such that it participates in the cycloaddition as the 2π component. A convenient way to construct the cyclohexenone is to make use of some aminodiene chemistry recently developed by Rawal. Consequently, the key amidofuran 13 was imagined to be derived from an appropriately substituted furan and diene 15 via an intermolecular [4+2]-cycloaddition.

Accordingly, the tert-butyloxycarbonyl protected 2-amidofuran 16a (R1, R2 = H) was first alkyted with 2,3-dibromopropene to give vinyl bromide 17 (Scheme 2).

\[ \text{Scheme 2}^{a} \]

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\begin{align*}
16a; R^1 & = R^2 = H \\
16b; R^1 & = Me, R^2 = H \\
16c; R^1 & = H, R^2 = Me \\
17; R & = Br \\
18; R & = CO_2Me \\
19 & \\
20 & \\
21a; R^1 & = R^2 = H \\
21b; R^1 & = Me, R^2 = H \\
21c; R^1 & = H, R^2 = Me \\
\end{align*}
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\text{Reagents: (a) NaH, 2,3-dibromopropene, DMF, 0 °C, 70%; (b) Pd(PPh_3)2, CO, i-Pr_2EtN, MeOH, 100 °C, 70%; (c) CH_2CN, Δ; (d) HF, 25 °C; (e) PhMe 2, (f) TFA, CH_2Cl_2, rt; (g) KOTMS, Et_2O, rt; (h) Pb(OAc)_2, } \text{DMF, 0 °C, 58%.}

Palladium-catalyzed carbylation of 17 in the presence of methanol provided the acryl derivative that was required for the intermolecular aminodiene cycloaddition reaction. Heating a mixture of 15 and 18 in CH_2CN at reflux for 2 h furnished a 2:1 mixture of diastereomeric amines 19.


that was immediately treated with HF at room temperature to unmask the enone 20. Because furan 20 slowly underwent an intramolecular Diels–Alder reaction during isolation attempts, the crude furan was simply heated at reflux in toluene for 30 min to effect the cycloaddition, ring opening, and dehydration cascade that provides the desired tricyclic ketone 21a. Although Danishefsky’s diene also participates in this sequence of events, higher temperatures (150 °C, sealed tube) and longer reaction times (12 h) were necessary to induce the intermolecular cycloaddition and lower overall yields (30%) of 21a were obtained from 18 using this diene. In a similar manner, amidofurans 16b18 and 16c19 were converted to dihydroindoles 21b and 21c.

Several features of this sequence are significant: The use of the aminodiene chemistry developed by Rawal and co-workers allows for the enantioselective synthesis of these ketones by selecting a chiral amine for the formation of a diene reactant analogous to 15.15a The carbamethoxy functionality, required to activate the olefin toward cycloaddition with 15, also serves as a protecting group that prevents the known aromatization of advanced ergoline intermediates to a naphthalene system.16b This sequence also allows for independent substitution of the aryl ring as in ketones 21b,c, a feature rarely exploited by other methodologies.

Ketone 21a was easily converted to Uhle’s ketone (6) by a three-step procedure without purifying any of the intermediates. Treatment of 21a with trifluoroacetic acid cleaved the carbamate group. This was followed by hydrolysis of the methyl ester with potassium trimethylsilylanolate so as to provide the potassium salt of the carboxylic acid.20 Finally, exposure of the crude salt to lead tetraacetate in wet DMF effected an oxidative decarboxylation to furnish 6 in 60% overall yield from 21a.21

The reactivity of 21a appears to be similar to that of 7. For example, when 21a was treated with phenyl-trimethylammonium tribromide (PTT) in THF,21 bromide 22 was isolated as a separable mixture (7:1) of diastereomers favoring the equatorial bromide in 85% yield.22 Interestingly, the bromide derived from 7 is exclusively isolated as the axial isomer 23,24 while 24, a similar substrate that possesses an angular methyl group, is only isolated as the equatorial bromide.11

(22) Stereochemical assignments are based upon coupling constants for the C(4) proton in each diastereomer.

Scheme 3

Ketone 21a was also transformed into triflate 25 in 89% yield by the action of triflic anhydride in the presence of 4-methyl-2,6-di-tert-butylpyridine. Subsequent cross coupling of 25 with N-methylpropiolamide23 could be accomplished via palladium catalysis to afford 26 in 87% yield. Alternatively, 25 could be carbonylated under CO atmosphere in the presence of methanol to provide diester 27 in good yield.

In summary, a novel method for constructing analogues of Kornfeld’s tricyclic ketone has been developed that relies on two sequential aminodiene Diels–Alder reactions to fashion the aromatic A ring. Investigation into the range of substituents that are allowed as well as the application of this methodology to the synthesis of ergot alkaloids is currently underway, and results will be disclosed in due course.

Acknowledgment. We thank the National Institutes of Health (GM59384 and GM60003) for generous support of this work. We acknowledge the use of shared instrumentation provided by grants from the NIH and NSF.

Supporting Information Available: Spectral characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.
OL0268992