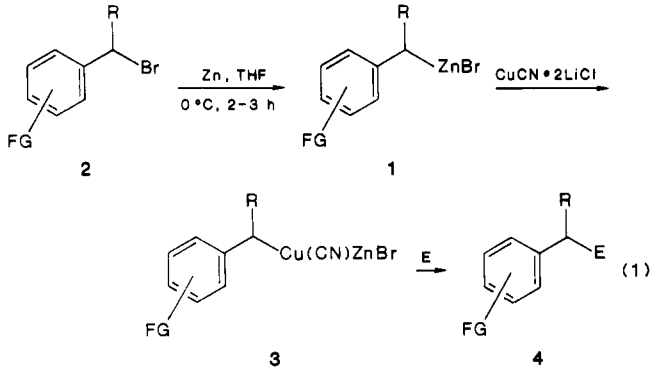
benzylic zinc bromides 1 in over 90% yield[10] (5 °C, 2–3 h; see eq 1 and Table I). Under our reaction conditions, only very small amounts of cross-coupling products (usually less than 5%) were observed with primary benzylic bromides. In the case of a secondary benzylic bromide (entry 15 of Table I), a slow addition (3.5 h) of (1-bromoethyl)benzene (10 mmol in 15 mL of THF) to activated zinc (2.5 equiv) at −15 °C was required to prepare the corresponding zinc derivative in 75% yield (20% of coupling products was formed). The reaction of (1-chloroethyl)benzene (10 mmol in 10 mL of THF) led to a further improvement. In this case, less than 8% of coupling products was formed and over 90% yield of the corresponding zinc compound could be obtained (2 equiv of Zn; 30 °C, 12–16 h; see entry 16 of Table I).



FG = COR, OAc, CN, Cl, I; E = aldehydes, acid chlorides, enones, allylic bromides; R = CH_3, H

The reactivity of 1 toward electrophiles E is considerably enhanced by performing a transmetalation to the copper derivatives **3** by using the new soluble copper salt[8] CuCN·2LiCl (see eq 1 and Table I). These copper species are highly stable below −20 °C but decompose slowly at higher temperatures. Reactions of **3** with various electrophiles afford very high yields of products **4** (85–97%). Allylic bromides react very rapidly (−70 to 0 °C, 5 min at 0 °C); see entries 4, 6, 9, and 13. The Michael addition of the copper reagents **3** to enones proceeds smoothly in the presence of Me_3SiCl[11] (2 equiv); see entries 2, 5, and 12. Without Me_3SiCl, enones react far more slowly and 3-iodo-2-cyclohexen-1-one selectively furnishes the corresponding unsaturated ketone (see entry 8) upon treatment with the (3-cyanobenzyl)copper derivative. Aldehydes react rapidly in the presence of BF_3·OEt_2[12] and afford secondary alcohols (see entries 1, 3, 7, 10, and 15). Finally, acid chlorides lead to the corresponding ketones in high yields (entries 11 and 14).

In conclusion, a general approach to highly functionalized benzylic zinc and copper organometallics is described and their good reactivity toward various organic electrophiles has been established. Extensions of this methodology are currently studied in our laboratory.

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Supplementary Material Available: Spectral data for new compounds (5 pages). Ordering information is given on any current masthead page.

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(10) Typical procedure: A solution of 21.5 mmol of the benzylic bromide in 11 mL of THF was slowly added (1 drop each 5 s) at 0 °C to 1.7 g (26 mmol) of cut zinc foil (99.99% purity) which had been activated with 200 mg of 1,2-dibromoethane. After 2–3 h of stirring at 5 °C, the benzylic zinc organometallic was ready to use. Ten millimoles of this solution was then added at −70 °C to a solution of 0.9 g (10 mmol) of CuCN and 0.9 g (21 mmol) of LiCl in 10 mL of THF. After warming up to −20 °C for 5 min, the reaction mixture was cooled to −70 °C and ready to use. (a) Reaction with acid chlorides and allylic bromides: A solution of 8 mmol (0.8 equiv) of the acid chloride or of the allylic bromide in 2 mL of THF was added at −70 °C. The reaction mixture was in the first case warmed up to −20 °C, stirred for 12 h at this temperature, and worked up. In the second case, the reaction mixture was slowly warmed up to 0 °C and worked up after 5 min. (b) Reaction with enones: Me_3SiCl (2.50 mL, 20 mmol) was added to the benzylic copper solution at −70 °C followed by 8 mmol (0.8 equiv) of the enone in 2 mL of THF. After 3 h at −70 °C, the reaction mixture was warmed up to −20 °C, stirred for 12 h at this temperature, and worked up as usual. (c) Reaction with aldehydes: BF_3·OEt_2 (2.50 mL, 20 mmol) was added to the benzylic copper solution at −78 °C, followed by 8 mmol (0.8 equiv) of the aldehyde in 2 mL of THF. The reaction mixture was warmed up to −30 °C, stirred for 4–6 h at this temperature, and worked up.

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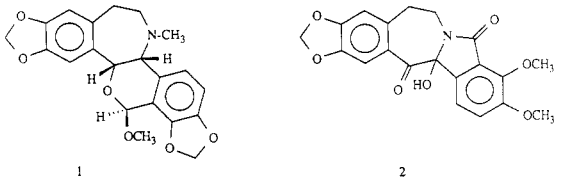
Oxidative Ring Expansion of Isoquinoline Enamides. Facile Formation of 3-Benzazepines

Summary: The reaction of enamides (acylenamines), derived from various substituted 1-methyl- and 1-ethyldihydroisoquinolines, with lead tetraacetate proceeds through an oxidative rearrangement to form 3-benzazepin-2-ones in high yield.

Sir: The benzazepine ring system occurs in the biologically active rhoeadine alkaloids, e.g., rhoeadine (**1**),[1] as well as in other isoquinoline-derived alkaloids like chilenine (**2**).[2]



1 2

Other simpler substituted benzazepines are being intensively developed as central nervous system and cardiovascular pharmaceutical agents.[3] Several approaches to the synthesis of this ring system have been described[4] and excellent methods exist for the preparation of aryl-substituted benzazepines.[3] However, benzazepines that are either unsubstituted or alkyl substituted on the azepine

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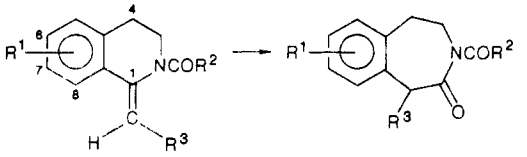
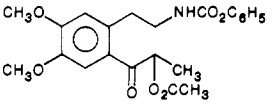
Table I. Pb(IV) Ring Expansion of Enamides



enamide	mp/bp, °C	R^1[a]	R^2	benzazepinone R^3	benzazepinone (yield, %)	benzazepinone mp/bp, °C
4	*b*	6,7-$(OCH_3)_2$	OC_2H_5	H	6 (76)	135.5–136.5
5	*g*	6,7-$(OCH_3)_2$	$OCH_2C_6H_5$	H	7 (91)	123.5–5.5
11	156 (0.08 mm)	6,7,8-$(OCH_3)_3$	OC_2H_5	H	12 (69)	96–97
13	153 (0.1 mm)	6,7-(OCH_2O)	OC_2H_5	H	14 (91)	106.5–107.5
15	*c*	5,6-$(OCH_3)_2$	OC_2H_5	H	16 (90)	98–99.5
17	*c*	6-OCH_3	OC_2H_5	H	18 (71)	150 (0.02 mm)
19	120 (0.01 mm)	H	OC_2H_5	H	20 (43)	145 (0.004 mm)
21	95–99	6,7-$(OCH_3)_2$	OC_6H_5	CH_3	22 (50)[d]	127–8
23	*e*	6,7-$(OCH_3)_2$	CH_3	H	24 (62)	116–8
25	*f*	6,7-$(OCH_3)_2$	2′,3′-$(OCH_3)_2C_6H_3$	H	26 (92)	201.5–202.5

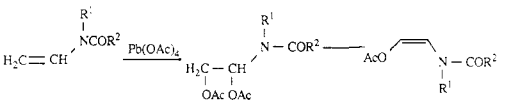
[a] Isoquinoline numbering. [b] Reference 12. [c] The enamide was purified by flash chromatography and used directly. [d] A 10% yield of i,



i

mp 105–9 °C was also obtained. [e] Reference 20. [f] Reference 21. [g] Reference 7.

Scheme I



portion are much less readily obtainable.[5] We describe a new oxidative rearrangement of isoquinoline enamides that furnishes functionalized benzazepines, rapidly and in high yield.

While the photochemistry of the enamides has been extensively investigated,[6] their ground-state reactivity with the exception of their use in the Diels–Alder reaction[6a] has been relatively unexplored.[6a,7] The oxidation of simple enamides shows similar reactivity patterns to that of enol ethers.[8] Analogously to enol ethers,[9] oxidation of enamide double bonds with lead tetraacetate (LTA) forms a diacetoxy derivative, which eliminates acetic acid to yield a β-acetoxy enamide (Scheme I), although other products are possible.[10,11] When the LTA oxidation of 1-methyleneisoquinoline enamides, readily obtained from the corresponding 1-methyl-3,4-dihydroisoquinolines, was investigated, the reaction took an unexpected course and led to a new, preparatively useful synthesis of benzazepinones.

Reaction of enamide **4**[12] with LTA in acetic acid instantaneously led to a single product, after glycerine quench, in 76% yield (Scheme II).[13] The mass spectrum indicated that the product **6** possessed an additional oxygen atom, and the ^1H and ^{13}C NMR spectra supported an N-substituted benzazepinone structure.[14] This was proved when the corresponding benzyl enamide **5** was oxidized to the benzazepine **7**. Catalytic removal of the benzyl group then yielded the known benzazepinone **8**.[15] A single-crystal X-ray analysis of the *N*-(2,3-dimethoxybenzoyl)benzazepinone (**26**) completed the structure proof of the rearrangement product.[16]

The mechanism of the rearrangement (Scheme II) proceeds through plumbation of the enamide double bond to form intermediate A, the same type of intermediate postulated in other enamide–LTA reactions.[10,11] However, in this case, as the intermediate fragments, the aromatic ring traps the incipient positive charge, forming the bridged

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(13) All new compounds possess physical spectra and combustion analyses consistent with the assigned structure.

(14) The benzazepinone **6** possesses: IR ($CHCl_3$) 1765, 1715 sh, 1705 cm^{-1}; ^1H NMR δ 6.63 (s, 2 H), 4.2–4.5 (m, 4 H), 3.99 (s, 2 H), 3.88 (s, 6 H), 3.20 (t, 2 H), 1.36 (t, 3 H); ^{13}C NMR 171.47 (s), 153.83 (s), 114.43 (d), 113.45 (d), 63.24 (t), 56.01 (q), 45.06 (t), 43.59 (t), 32.75 (q), 14.25 (q); MS, *m/e* (relative intensity) 293 (parent, 100), 247 (92), 191 (42), 177 (38).

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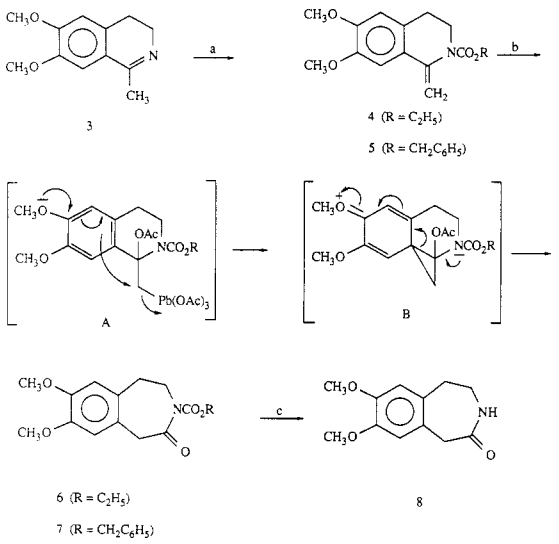
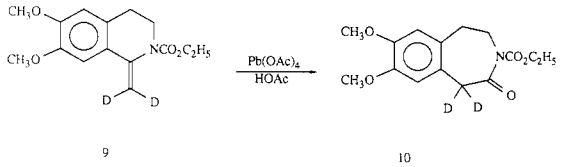
(16) Compound **26** crystallized, by slow evaporation of a saturated solution in methylene chloride, in the orthorhombic system, space group *Pca*2 (No. 29), with a = 15.035 (2) Å, b = 7.674 (2) Å, c = 33.385 (4) Å; V = 3852 (1) Å^3, Z = 8, D_x = 1.33 g/cm^3. X-ray reflection measurements (Cu Kα), on a crystal of dimensions 0.5 × 0.2 × 0.2 mm, were made on 2664 unique reflections with indices $h,k,-l$, for $2\theta \leq 120°$; 1470 reflections had $F_o \geq 6\sigma(F_o)$. The space group was identified from the observed systematic extinctions. The structure was solved by using direct methods and Fourier techniques. Full matrix least-squares refinement of 504 variables using 1464 reflections with $F_o > 6\sigma(F_o)$ converted with residual R = 0.047 and R_w = 0.057. Atomic parameters and observed and calculated structure factors are included in the supplementary material.

Scheme II[a]



[a] Reagents: (a) diethyl pyrocarbonate (for **4**); ref 7 for **5**; (b) lead tetraacetate/acetic acid; (c) Pd/H_2 (for **7**).

Scheme III



intermediate B that can then ring open to the observed benzazepinone. This mechanism predicts migration of the aromatic ring from C-1 of the isoquinoline ring to the exocyclic methylene group in **4**, which after LTA oxidation becomes the methylene group in **6**. This was proved by deuterium labeling (Scheme III). Oxidation of the enamide **9**, deuteriated on the exocyclic methylene group, yielded the benzazepine **10**, where the deuterium is now found on the methylene group between the aromatic ring and azepinone carbonyl group.[17] Equivalent results were also obtained when the exocyclic methylene group in **4** was ^{13}C-labeled. The olefinic methylene signal in **4** (δ 102.2) shifted to δ 45.1, the signal for the methylene group in **6**. This type of rearrangement has precedence in the LTA oxidative rearrangement of certain styrenes;[8,18] however the LTA oxidation of acetophenone enol ethers does not induce a rearrangement.[19]

A representative selection of the isoquinoline enamides studied is collected in Table I. A variety of electron-releasing substituents in various positions on the aromatic ring can be accommodated; even the unsubstituted enamide **19** forms the corresponding benzazepinone **20** in reasonable yield. The nature of the carbonyl substituent, alkoxycarbonyl, acyl, or aroyl, does not have an effect (cf ref. 11), and the ethylidene enamide **21** forms the corresponding methyl-substituted benzazepinone **22**. In summary, LTA oxidation of 1-methylene- and 1-ethylideneisoquinoline enamides in acetic acid forms benzazepinones rapidly and in high yield by a novel rearrangement, making these compounds easily accessible from readily available precursors.

Acknowledgment. The author would like to thank Prof. Paul Margaretha, Universität Hamburg, for suggesting the ^{13}C experiment, as well as Dr. E. Ezell of BOC for conducting the X-ray analysis of **26**.

Supplementary Material Available: Representative procedures for the oxidative ring expansion of enamides **5** and **25** and the formation of benzazepine **8**, together with spectral data for all compounds and X-ray data for compound **26**, containing positional and thermal parameters (35 pages). Ordering information is given on any current masthead page.

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(17) Prepared by deuterium exchange of the methyl protons in **3** using D_2O. Deuteriated **9** possessed 90% D_2, 9% D_1. Benzazepinone **10** retained 56% D_2, 31% D_1 by MS and NMR spectroscopy.

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A Divergent de Novo Synthesis of Carbohydrates Based on an Accelerated Inverse Electron Demand Diels–Alder Reaction of 1-Oxa-1,3-butadienes

Summary: A divergent, de novo synthesis of selectively protected carbohydrates based on the accelerated and productive $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction of β,γ-unsaturated α-keto esters [e.g., methyl *trans*-4-methoxy-2-oxo-3-butenoate (**1**)] with electron-rich dienophiles (e.g., **2a,b**) is detailed.

Sir: The 4π participation of simple α,β-unsaturated aldehydes and ketones, electron-deficient heterodienes bearing a terminal oxygen atom, in $LUMO_{diene}$-controlled Diels–Alder reactions typically suffers from low conversions, competitive polymerization, and harsh reaction conditions.[1-3] A limited number of 1-oxa-1,3-butadiene structural variations and modified reaction conditions have been successfully introduced that have permitted the productive 4π participation of α,β-unsaturated carbonyl compounds in [4 + 2] cycloaddition reactions[3-6] and in-

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(4) 1-Oxa-1,3-butadienes bearing a C-3 electron-withdrawing substituent: Tietze, L. F. In *Selectivity-A Goal for Synthetic Efficiency*; Trost, B. M., Bartmann, W., Eds.; Verlag-Chemie: Weinheim, 1984; pp 299–315. See also ref 2.

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