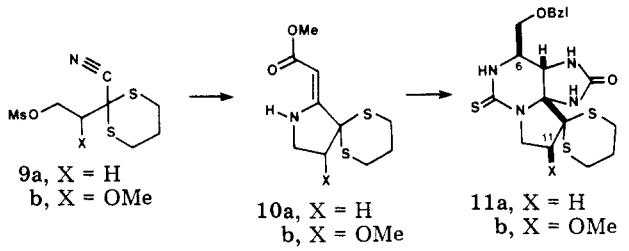
Scheme II



silica gel. Column chromatography on solvent-wetted SiO_2 was an effective procedure for isolating pure enamino ester. Note that it was crucial to use the prescribed volumes of THF and K_2CO_3 solution. Otherwise, emulsions would form and the clear, Zn^{2+}-free THF layer would not separate, making the workup tedious and decreasing the yield. For each mole of zinc salt produced, the cooled reaction mixture should be diluted to a total volume of 3 mL, and then $^1/_3$ mL of 50% aqueous K_2CO_3 should be added with vigorous stirring.

General Procedure for the Preparation of β-Keto Esters 4. The THF solution of crude enamino ester obtained as described above was subjected to acid hydrolysis as follows. The THF solution was treated with 1 mL of 10% aqueous HCl at room temperature for 30 min, or a time sufficient for the UV-active enamino ester to be no longer detectable by TLC. The mixture was concentrated, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and purified by PTLC (SiO_2 developed with 1:1 hexanes:Et_2O, typically) to yield the pure β-keto ester.

Synthesis of 10b. A suspension of 16.0 g (5 equiv) of activated zinc dust in 150 mL of THF was heated to reflux under N_2. Several 0.1-mL portions of methyl bromoacetate were added with vigorous stirring to initiate the reaction. When the green color appeared, 14.55 g (49.0 mmol) of cyano mesylate **9b** in 50 mL of THF were added. Then 18.9 mL (4 equiv) of methyl bromoacetate were added dropwise over 45 min to the refluxing mixture. The mixture was refluxed 10 min longer, cooled to room temperature, diluted with 430 mL of THF, and quenched with 70 mL of 50% aqueous K_2CO_3. Rapid stirring for 45 min gave two distinct layers. The THF layer was decanted, and the residue was rinsed with THF. The combined THF layers were dried over $MgSO_4$ and concentrated. This crude intermediate was then stirred with 14 g of powdered K_2CO_3 in 150 mL of DMF for 14 h. The reaction mixture was diluted with 150 mL of Et_2O, filtered through Celite, concentrated, and adsorbed on Florisil. The Et_2O eluate was concentrated and purified by MPLC (1.5:1 Et_2O:hexanes), giving 10.66 g (38.8 mmol, 79%) of 10b as colorless crystals from hexanes/EtOAc, mp 117–118 °C.

A procedure almost indentical with the above was used for the synthesis of 8 and **10a**.

Acknowledgment. Financial support from the National Institutes of Health (Grant No. NS 12108) and the National Science Foundation (Grant No. CHE 78-06296) is gratefully acknowledged.

Registry No. **1a**, 96-32-2; **1b**, 5292-43-3; **1e**, 5445-17-0; **2a**, 6280-87-1; **2c**, 64273-86-5; **2d**, 100-47-0; **3a**, 86971-58-6; **3b**, 86971-59-7; **3c**, 86993-51-3; **3d**, 86971-60-0; **3e**, 66213-66-9; **3f**, 86971-61-1; **4a**, 22977-45-3; **4b**, 86971-62-2; **4c**, 86971-63-3; **4d**, 614-27-7; **4e**, 29540-54-3; **4f**, 86971-64-4; **5** (X = Br), 86993-49-9; **5** (X = OMs), 86993-50-2; **6**, 86971-65-5; **7**, 52909-60-1; **8**, 86971-66-6; **9a**, 86971-67-7; **9b**, 86971-68-8; **10a**, 86971-69-9; **10b**, 86971-70-2; **11a**, 87037-54-5; **11b**, 86971-71-3; $N{\equiv}CC(Me)_2CH_2CH_2OMe$, 86971-72-4; $THPOCH_2CHO$, 699-13-8; $[O_3SS(CH_2)_3SSO_3]^{2-}{\cdot}2Na^+$, 37914-69-5; 2-cyano-1,3-dithiane, 33927-42-3; ethylene oxide, 75-21-8; saxitoxin, 35523-89-8; gonyautoxin, 77462-64-7.

Supplementary Material Available: Spectroscopic and crystallographic data and tables listing representative examples of the Blaise reaction (42 pages). Ordering information is given on any current masthead page.

Synthesis of Oxazolo[4,3-*a*]isoquinoline and Related Compounds through Intramolecular Arylation of α-Oxaacyl Iminium Ions

Shinzo Kano,* Yoko Yuasa, Tsutomu Yokomatsu, and Shiroshi Shibuya

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Received January 27, 1983

π cyclization of *N*-acyl iminium ions has proven to be an important synthetic method for a wide variety of heterocyclic systems.[1] Several kinds of *N*-acyl iminium ions (**1a–f**) have been used for this purpose. Cyclization of **1d** and **1e**, followed by desulfurization of the cyclization products, is a valuable method for synthesis of α-substituted N-heterocycles.[1i] Recently, imidazo[2,1-*a*]isoquinolines were also obtained by annelation of imidazolidinones.[1j] We have now examined cyclization of α-oxaacyl iminium ions **1g** to provide oxazolo[4,3-*a*]isoquinolines and related compounds (Schemes I and II).

Starting materials **4a–g** were prepared by coupling the oxazolidinediones **2**, **3a**,[2] or **3b**[3] with the appropriate arylethanol by using the Mitsunobu procedure[4] with diisopropyl azodicarboxylate. Reduction of **4a–g** (DIBAH, toluene, −78 °C, 1 h) followed by treatment of the corresponding reduction products, without purification, with formic acid yielded the corresponding cyclization products **5a–g**, respectively, in moderate yields (Table I, Scheme III). In the formation of **5c–e,g**, arylation proceeded with high stereoselectivity. In the case of **5c**, thenylation proceeded from the side opposite the methyl group, and formation of the alternative stereoisomer was not observed. The ^1H NMR spectrum of **5a** exhibited two singlets attributable to 1-CH_3 in a different region (δ 0.97 and 1.76). The CH_3 cis to the benzene ring resonates at a higher field stemming from the shielding effect of the benzene ring. The trans-oriented CH_3 resonates at lower field because of the deshielding effect of benzene ring. In the case of **5g**, the higher 1-CH_3 signal disappeared and only the lower 1-CH_3 signal (δ 1.69, d, J = 6 Hz) remained. This fact strongly indicates that phenylation proceeds from the side opposite the methyl group and that the relative configuration of 1-H and 10b-H in **5g** is trans. Similarly, the relative configuration of **5d** and **5e** is also indicated to be trans. Reduction of **5d** ($LiAlH_4$, THF, room temperature) gave the trans-oriented 1-(α-hydroxybenzyl)isoquinoline **6** (Scheme IV). Although reduction of 1-benzoylisoquinoline **8** gives the 1-(α-hydrobenzyl)isoquinoline **7**,[5] the stereoisomer of **6**, the stereochemistry of **7** has not been determined. The stereochemistry of **5f**, obtained as a single product from one isomer of **4f**, was not determined from its spectral data at this stage.

(1) (a) Dijkink, D.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 935. (b) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. (c) Speckamp, W. N.; Veenstra, S. J.; Dijkink, D.; Fortgens, R. *J. Am. Chem. Soc.* **1981**, *103*, 4643. (d) Veenstra, S. J.; Speckamp, W. N. *Ibid.* **1981**, *103*, 4645. (e) Dijkink, D.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 173. (f) Hart, D. G. *J. Org. Chem.* **1981**, *46*, 367. (g) Hart, D. G. *Ibid.* **1981**, *46*, 3576. (h) Nossin, P. M. M.; Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, *23*, 3807. (i) Hamersma, J. A. M.; Speckamp, W. N. *Ibid.* **1982**, *23*, 3811. (j) Kohn, H.; Liao, Z.-K. *J. Org. Chem.* **1982**, *47*, 2787.

(2) Aspelund, H. *Suom. Kemistiseuran Tied.* **1940**, *49*, 42.

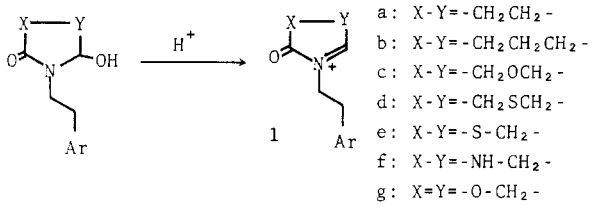
(3) Shapiro, S. L.; Rose, I. M.; Roskin, E.; Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 386.

(4) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(5) MacMahon, R. M.; Thormer, C. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2163.

0022-3263/83/1948-3835$01.50/0

Scheme I



Scheme II

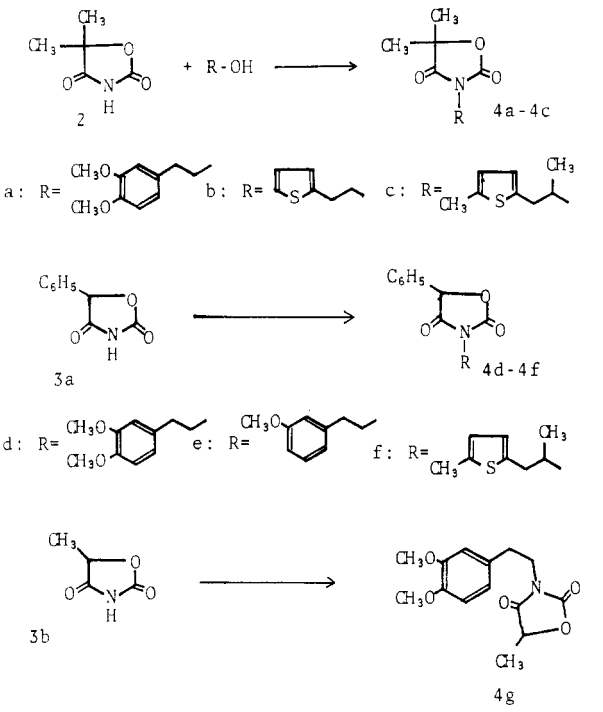


Table I. Yields and Physical Data of 4a-f and 5a-g[a]

compd	yield, %	mp, °C	m/e (M+)	formula
4a	70	99-101	293	$C_{15}H_{19}NO_5$
4b	68	68-70	239	$C_{11}H_{13}NO_3S$
4c	65	oil	267	$C_{13}H_{17}NO_3S$
4d	68	167-168	325	$C_{19}H_{19}NO_5$
4e	70	79-81	311	$C_{18}H_{17}NO_4$
4f[b]	27	101-103	315	$C_{17}H_{17}NO_3S$
4g	63	109-111	279	$C_{14}H_{17}NO_5$
5a	60	146-148	277	$C_{15}H_{19}NO_4$
5b	63	134-136	223	$C_{11}H_{13}NO_2S$
5c	68	123-125	251	$C_{13}H_{17}NO_2S$
5d	70	167-169	325	$C_{19}H_{19}NO_4$
5e	65	129-131	295	$C_{18}H_{17}NO_3$
5f	38	138-140	299	$C_{17}H_{17}NO_2S$
5g	73	96-98	263	$C_{14}H_{17}NO_4$

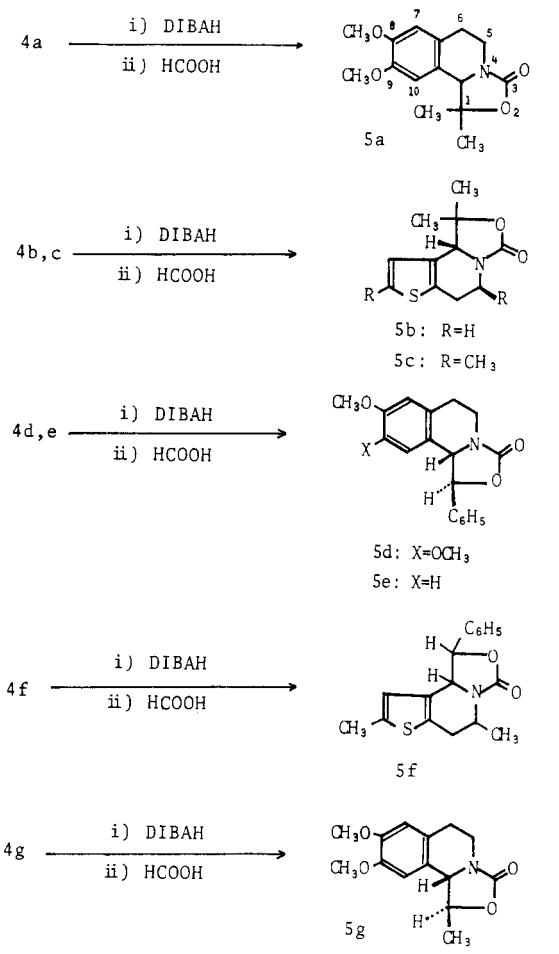
[a] Satisfactory analyses (±0.4% for C, H, and N for all compounds except 4c). [b] This compound was obtained as a diastereoisomeric mixture (3:2; 67%). The data shown here are those of one isomer obtained as a pure crystalline form by recrystallization.

Experimental Section

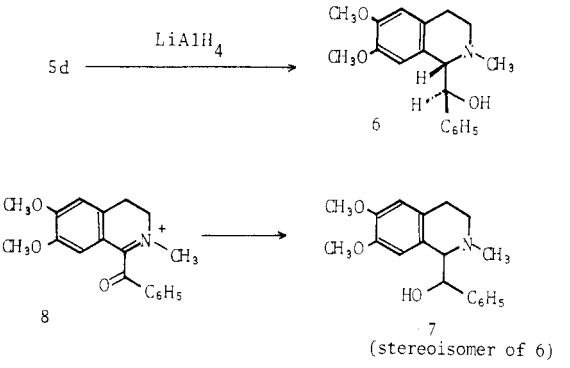
General Methods. Melting points are uncorrected. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian EM-390 instrument. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Hitachi RMU-7L instrument. THF was distilled from $LiAlH_4$ before use. Toluene was dried over CaH_2 under reflux and distilled before use. Formic acid used in this study was of the best commercial grade available. All reactions were carried out under N_2 unless otherwise noted.

General Procedure for Synthesis of 4a–g. To a stirred mixture of **2** (2.58 g, 20 mmol) for the synthesis of **4a–c**, of **3a** (3.54 g, 20 mmol) for the synthesis of **4d–f**, or of **3b** (2.30 g, 20 mmol) for the synthesis of **4g**, triphenylphosphine (5.2 g, 20 mmol), alcohol (20 mmol), and THF (30 mL) was added a solution of diisopropyl azodicarboxylate (4.04 g, 20 mmol) in THF (20 mL) under ice cooling. After the stirring had been continued for 14 h at room temperature, the solvent was evaporated. The resulting residue was chromatographed on silica gel (30 g) by using benzene–hexane (1:1) as an eluent. The products were collected by monitoring with TLC to give **4**. Yields and physical data are given in Table I.

Scheme III



Scheme IV



General Procedure for Synthesis of 5a–g. To a stirred solution of **4** (10 mmol) in toluene (40 mL) was added diisobutylaluminum hydride (2.84 g, 13.1 mL of 25% toluene solution, 20 mmol) at −78 °C. After the stirring had been continued for 1 h at the same temperature, the mixture was decomposed with 5% H_2SO_4 (50–60 mL) and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated. The remaining residue, without purification, was treated with formic acid (20 mL) at room temperature for 14 h. The mixture was made

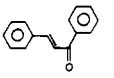
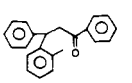
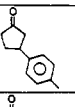
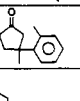
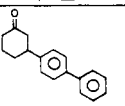
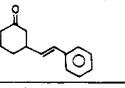
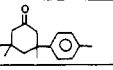
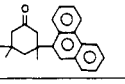
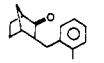
basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated. The remaining residue was chromatographed on silica gel (10 g) by using benzene as an eluenet. Removal of the solvent gave **5**, which was recrystallized from methanol–ether. Yields and physical data are listed in Table I.

1,2,3,4-Tetrahydro-1-(α-hydroxybenzyl)-6,7-dimethoxy-2-methylisoquinoline (6). To a stirred suspension of $LiAlH_4$ (200 mg, 5.4 mmol) in THF (40 mL) was added a solution of **5d** (400 mg, 1.23 mmol) in THF (10 mL) at room temperature. After the stirring had been continued for 14 h, the mixture was decomposed with 10% NaOH. Inorganic precipitate was removed by filtration, and the solvent was evaporated. The remaining residue was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residual solid was recrystallized from methanol–ether to give **6**: 293 mg (76%); mp 155–157 °C; ^1H NMR ($CDCl_3$) δ 2.58 (3 H, s), 3.13–3.63 (4 H, m), 3.27 (3 H, s), 3.42 (1 H, d, J = 9 Hz), 3.84 (3 H, s), 4.23 (1 H, d, J = 9 Hz), 5.39 (1 H, s), 6.61 (1 H, s), 7.37 (5 H, br s); mass spectrum, m/z 314 (MH^+) (electron-impact mass spectrum did not give M^+), m/e 206 (M^+ - C_6H_5CHOH). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.64; H, 7.46; N, 4.29.

Registry No. **2**, 695-53-4; **3a**, 5841-63-4; **3b**, 27770-23-6; **4a**, 86970-73-2; **4a** reduction product, 86970-74-3; **4b**, 86970-75-4; **4b** reduction product, 86970-76-5; **4c**, 86970-77-6; **4c** reduction product, 86970-78-7; **4d**, 86970-79-8; **4d** reduction product, 86970-80-1; **4e**, 86970-81-2; **4e** reduction product, 86970-82-3; (*R**,*R**)-**4f**, 86970-84-5; (*R**,*S**)-**4f**, 86970-83-4; **4f** reduction product, 86970-85-6; **4g**, 86970-86-7; **4g** reduction product, 86970-87-8; **5a**, 86970-88-9; **5b**, 86970-89-0; **5c**, 86970-90-3; **5d**, 86970-91-4; **5e**, 86970-92-5; **5f**, 86970-93-6; **5g**, 86970-94-7; **6**, 86970-95-8; 3,4-dimethoxybenzeneethanol, 7417-21-2; 2-thiopheneethanol, 5402-55-1; α,5-dimethyl-2-thiopheneethanol, 86970-96-9; 3-methoxybenzeneethanol, 5020-41-7.

Supplementary Material Available: A listing of spectral data of compounds **4a–g** and **5a–g** (1 page). Ordering information is given on any current masthead page.

Table I

Entry	α-enone	Ar-X	1-4 adduct	% isolated yield in THF	yield in ether	yield lit.
1				98		70[a]
2				73	57	b
3				polymers	76	
4				polymers	72	20[c]
5				92		
6				84		
7				70	94	
8				76		
9				79		

[a] via a phenyl copper reagent addition. See Ref 15; [b] 49–66% yields were obtained in similar cases from arylzinc additions. See Ref 13d; [c] See Ref 16.

Ultrasound in Organic Synthesis. 4.[1] A Simplified Preparation of Diarylzinc Reagents and Their Conjugate Addition to α-Enones

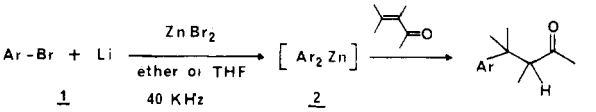
Jean-Louis Luche,* Christian Petrier, Jean-Philippe Lansard, and Andrew E. Greene

Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité, Université Scientifique et Médicale de Grenoble, BP 68 38402 St. Martin d'Heres Cedex, France

Received February 14, 1983

We have previously demonstrated that sonication[2] of organic halides with lithium metal in an ethereal solvent constitutes an exceptionally rapid and easy procedure for obtaining the corresponding lithio derivatives. These reagents readily react in situ with various organic (aldehydes, ketones,[3] dimethylformamide[1]) as well as inorganic (cuprous iodide[4]) species.

We now report a very simple preparation of diarylzinc derivatives by this method and their subsequent, generally high yield, reaction with conjugated enones.[5] The transmetalation reactions of organolithium and organomagnesium derivatives with zinc halides have proven to be among the most synthetically useful methods for producing organozinc reagents.[6] We have found that the preparation of diverse diarylzinc reagents **2** can be readily achieved in a one-pot process by sonication of the aryl bromides **1** in the presence of lithium wire and zinc bromide in dry ether or tetrahydrofuran (eq 1). The



(1)

reaction is usually complete within 30–45 min at 0 °C, as evidenced by the total disappearance of the metal.[7] Side reactions such as Wurtz coupling appear to be minimal under these conditions. Sonication is essential in this step;[8] much slower and less efficient reactions are observed on lowering the energy output of the sonicator and on replacing the sonication by magnetic stirring (3 h at room temperature in the case of *p*-bromotoluene).

Conjugate addition of these sonically prepared zinc reagents to various α-enones can be easily effected at room temperature in the presence of nickel acetylacetonate

(1) For the previous paper, see: Petrier, C.; Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1982**, *23*, 3361.

(2) For recent papers on sonochemical reactions, see: (a) Han, B. H; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030. (b) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, 1453.

(3) Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926.

(4) Luche, J. L.; Petrier, C.; Gemal, A. L.; Zikra, N. *J. Org. Chem.* **1982**, *47*, 3805.

(5) The conjugate addition of reagents obtained from alkyl and vinylic bromides has not yet been optimized.

(6) See, for example: (a) Thiele, K. H.; Dimitrov, V.; Thielemann, J.; Brueser, W.; Zschunke, A. *Z. Anorg. Allg. Chem.* **1981**, *483*, 154. (b) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, **1974**; p 249.

(7) The black mixture contains a reactive organozinc species, the exact nature of which has not yet been investigated. The stoichiometry of the reaction, however, corresponds to the formation of a diarylzinc compound. The presence in the reaction medium of lithium bromide (4 equiv/Ar_2Zn) should have an effect on the reactivity. For related examples, see: Jones, P. R.; Goller, S. L.; Kauffman, W. J. *J. Org. Chem.* **1969**, *34*, 3566.

(8) The mechanism by which the sonic waves promote the reaction probably does not involve cavitational effects. These effects appear to be unlikely in solvents such as ether. See, for example: Frenkel, J. *Acta Physico Chim. URSS* **1940**, *12*, 317.

0022-3263/83/1948-3837$01.50/0