Synthetic Photochemistry with Heterocyclic Anilides. Stereochemistry of the Intramolecular 1,5-Hydrogen Shifts in Nonoxidative Photocyclization of Benzo[*b*]thiophene-2-carboxanilides[1,2]

Summary. Photocyclization of benzo[*b*]thiophene-2-carboxy-*N*-methylanilide yielded 1-benzothiophene[2,3-*c*]-*trans*-14,15-dihydro-5-methylquinolin-6-one, while the lower homologous anilide gave 1-benzothiophene[2,3-*c*]-*cis*-14,15-dihydroquinolin-6-one by two distinct mechanisms. The structures were determined by single-crystal Roentgen-ray analysis.

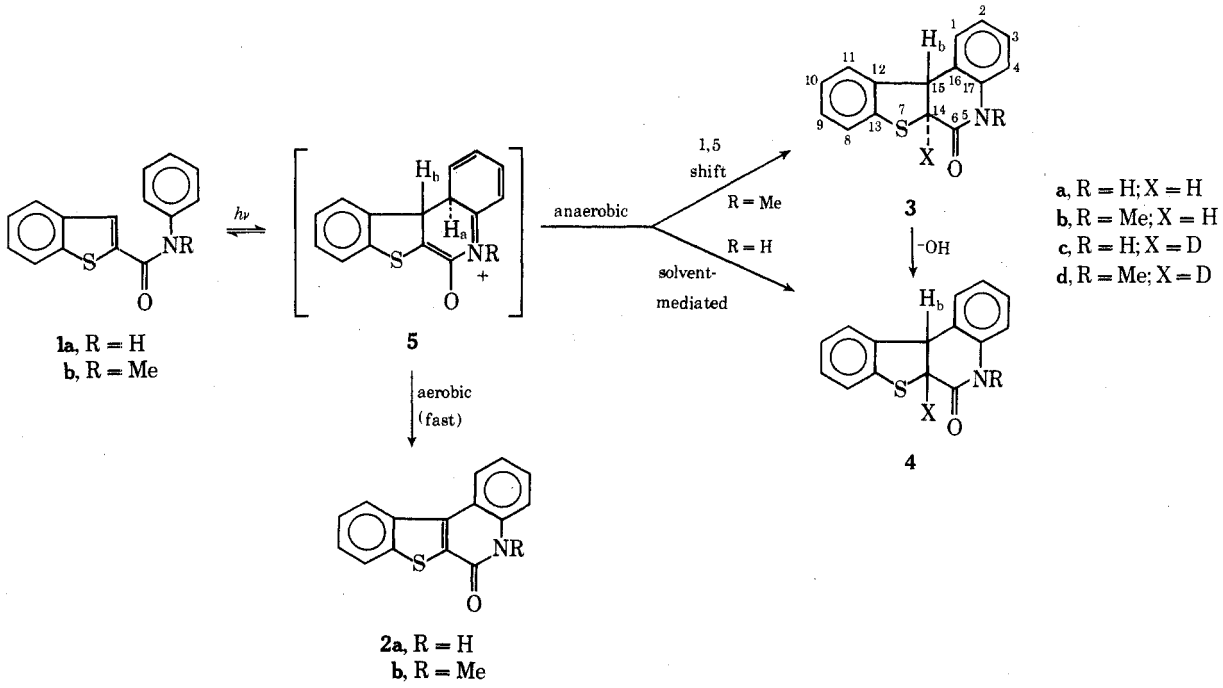
Sir: Heterocyclic anilides, such as benzo[*b*]thiophene-2- (**1a**) and indole-2-carboxanilide, undergo photocyclization in the presence of dissolved oxygen to afford the heterocyclic-condensed quinolones (**2a**, etc.).[3] Whereas *oxidative* cyclizations of anilide systems[1,3,4] are closely related to the well-known photoreactions in the stilbene series,[5] Chapman et al. observed nonoxidative photocyclization of *N*-arylenamines.[6] Recently Ninomiya et al. have also studied similar nonoxidative reactions of enamides.[7] This report focuses on the stereochemical aspects involving the trans adduct intermediate **5** in the photocyclization of certain anilides as well as on the synthesis of novel heterocycles based on variations of the experimental conditions.

On irradiation[8] in a mixture of benzene and ethanol (10:1 v/v, 200 mg/20 ml) for 2 hr, **1a** cyclized oxidatively to **2a** (mp >310°, 45% yield), which was accompanied by a crystalline product **4a** (mp 250–251°, 15%) with the same composition as the starting material **1a** [*m/e* 253 (M^+)]. When the reaction was performed under a stream of nitrogen in a solvent free of oxygen, **4a** was obtained as the major product (50%) along with a trace of **2a.** Under the anaerobic conditions,[8] its *N*-methyl derivative **1b** also afforded the nonoxidative product **3b** (mp 168–169°, 52%). The relative

Table I
Physical Data

	3b	4a
Molecular formula	$C_{16}H_{13}NSO$	$C_{15}H_{11}NSO_3$
Crystal size	~(0.55 × 0.58 × 0.19) mm	~(0.13 × 0.38 × 0.68) mm
Space group	$P2_1/a$	$P\bar{1}$
a	10.258 (6) Å	8.300 (4) Å
b	14.518 (9) Å	10.768 (8) Å
c	8.898 (5) Å	7.957 (4) Å
α		110.2 (1)°
β	104.9 (2)°	73.7 (1)°
γ		100.8 (1)°
Z	4	2
d_{calcd}	1.39 gm/cc	1.49 gm/cc
Max U.R	5.7	8.2
Mounting axis	$\bar{1}20$	$\bar{1}1\bar{2}$
Data collection	Automatic diffractometer θ–2θ scan technique Cu Kα (λ = 1.54178 Å)	
Number of independent reflections	2074	1574

stereochemistry of H_b and 14 H in **3b** and **4a** was not immediately apparent since the NMR of **4a** had only a singlet (2 H, 4.78 ppm) for the two hydrogens, although that of **3b** had an AB-type coupling. However, when **3b** was reduced to the deuterated amine [*O*-d_2, mp 102–103°, *m/e* 255 (M^+)] the NMR spectrum showed characteristic peaks for H_a at 4.16 ppm (1 H, d, J = 13 Hz) and H_b at 3.60 (1 H, d, J = 13 Hz) suggestive of trans ring fusion.[6] The complete structure of **3b** was directly established by X-ray analysis.[9] In a similar manner the structure of **4a** was determined using the sulfone derivative (mp >320°) prepared by oxi-



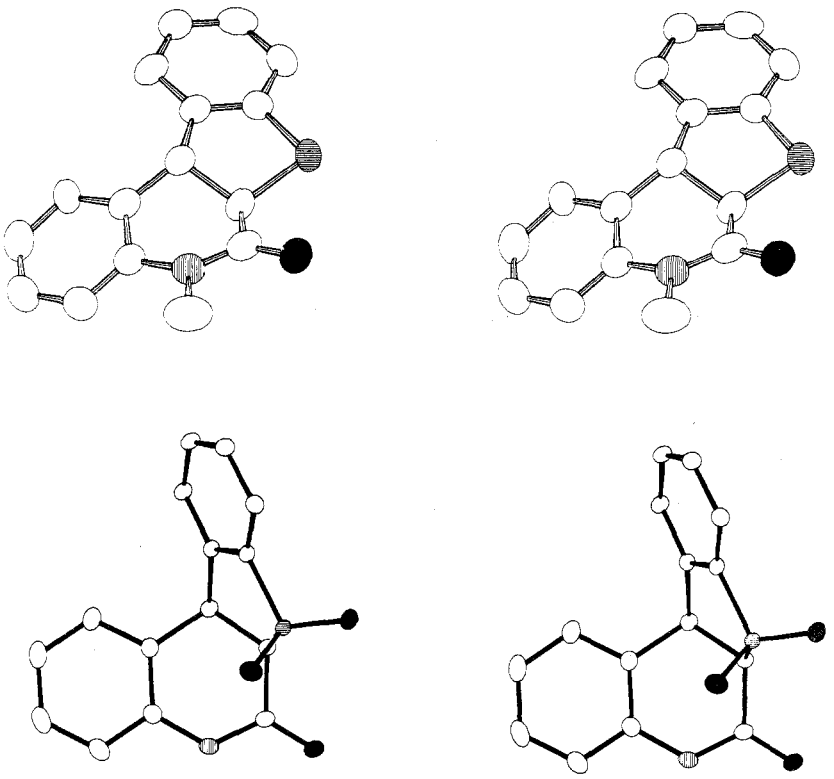


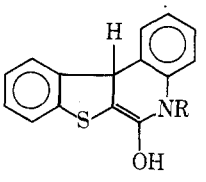
Figure 1. Top: Stereodiagram of 1-benzothiophene[2,3-*c*]-*trans*-14,15-dihydro-5-methylquinolin-6-one (**3b**). Bottom: Stereodiagram of 1-benzothiophene[2,3-*c*]-*cis*-14,15-dihydroquinolin-6-one (**4a**) sulfone. In both cases the sulfur is labeled ○, the nitrogen is labeled ○, and the oxygens are labeled ●. The figures were drawn by computer using program ORTEP written by C. K. Johnson of Oak Ridge National Laboratory, Oak Ridge, Tenn (1965).

dation (0.3% H_2O_2 in formic acid) of **4a** (see Table I and Figure 1). Careful product analysis showed that **3b** was accompanied by a small amount of **4b** (mp 168–169°), but **3a** was not detected in the reaction mixture from **1a.** The cis structure of **4b** was confirmed by methylation of **4a** with methyl iodide and sodium hydride. It is noteworthy that the *N*-H anilide **1a** produces the cis product **4a,** while the *N*-methyl anilide **1b** mainly gives the trans isomer **3b.** Although **4a** was converted into **2a** by oxidation with iodine, it is unlikely to be the true intermediate in the phototransformation (**1a** → **2a**), because on irradiation under aerobic conditions **4a** and **3b** afforded **2a** and **2b,** respectively, but at a lower rate than by the direct transformation (**1b** → **2b**). Thus **3b** and **4a** must be the products arising from a plausible intermediate, such as **5,** as a result of a process that competes with the direct oxidation to **2.**

Regardless of the details of the hydrogen shift, the trans junction in **3b**[9] requires the trans configuration for **5** in the initial bond formation process from **1b** consistent with simple HMO calculation, *i.e.,* the conrotatory course for the photochemical electrocyclic reaction and the subsequent thermally allowed sigmatropic suprafacial 1,5-hydrogen shift.[10] Anaerobic irradiation of anilide-*2,3,4,5,6-d*$_5$ **1b** gave **3d** (*1,2,3,4-d*$_4$, mp 165–166°) in which X (trans) contained >90% of deuterium in support of the intramolecular 1,5 shift of H_a subsequent to cycloaddition, at least in aprotic media, as the major pathway for the overall formation of **3b.** This example illustrates the principle of conservation of orbital symmetry for an arylanilide 6-π-electron system undergoing photocyclization.

In the course of the hydrogen shift from **1a,** rapid hydrogen exchange of N–H occurs and significant interaction between the medium, involving the imide carbonyl, must be considered. Indeed, irradiation of **1a** under anaerobic conditions in acetonitrile containing 10% D_2O afforded **4c** in 76% yield, demonstrating that the cis-14-H comes almost exclusively from the protons of the medium. The same treatment of **1b** gave a mixture of **3b** (28%) and **4d** (34%). These results confirm that the trans-14-H originates definitely from the internal source, and the cis-14-H is incorporated from the medium. Neither irradiation nor refluxing of **4a** and **4b** in the above solvents formed **4c** and **4d,** respectively, indicating that the cis-14-H (D) of **4a,b** is primarily established during and not after the process of the H shift. The cis structures are more stable than the trans. For example, when a solution of **3b** in 10% NaOH–tetrahydrofuran was allowed to stand at room temperature for 12 hr, nearly 80% **4b** was isolated. The analogous reaction with 10% NaOD formed **4d** showing that enolization favors the formation of the cis isomer.

A plausible mechanism for the formation of **4a** from **1a** may involve a "solvent-mediated" pathway in which the amide carbonyl participates, presumably, resulting in the intervention of an "enol" **6** (R = H). Such an enol would



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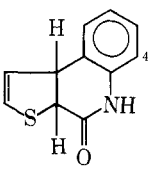

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lead preferably to the cis isomer **4.** Irradiation of **1b** (benzene, 10^{-3} *M*) in the presence of 1,2-cyclohexadiene quenched the formation of **3b** with a linear Stern–Volmer plot up to 0.1 *M* of the quencher, suggestive of a triplet-state intermediate for the cyclization.

In the stilbene series[5] *trans*-dihydrophenanthrene intermediates, analogous to **5,** have been postulated but proven only in a few cases.[11] The five-membered heteroaromatic anilide system is novel and useful in that it permits the separation of oxidative and nonoxidative pathways. In ad-

dition, on a preparative scale a variety of heterocyclic condensed dihydroquinolone systems have now become accessible; for example, **7** (mp 197–199.5°) was obtained by the nonoxidative photocyclization of thiophen-2-carboxanilide in 56% yield. Synthetic applications of the method to other heterocyclic systems including furan, pyrrole, and their benzo derivatives are in progress.

References and Notes

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(8) All new compounds gave satisfactory analyses, and their structures were supported by spectral (uv, ir, NMR, mass) data. Irradiation under aerobic conditions was performed in a Pyrex immersion well fitted with a 100-W high-pressure mercury lamp as a light source. For experiments under anaerobic conditions a substrate solution in acetonitrile (10 m*M*) was degassed in a Pyrex tube, sealed, and irradiated with a 500-W high-pressure mercury lamp.
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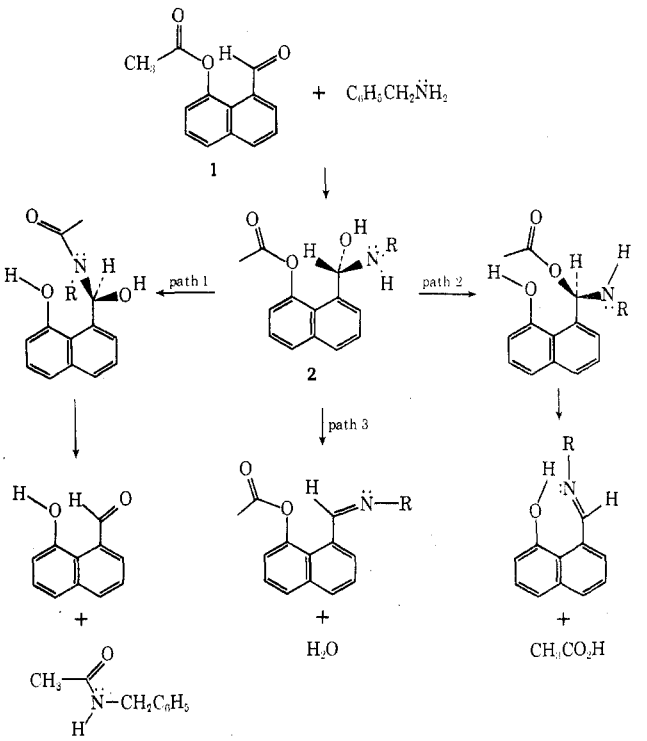
Rapid Intramolecular Acyl Transfer from Phenol to Carbinolamine—Progress toward a New Class of Peptide Coupling Reagent

Summary: Benzylamine and amino acid esters react with 8-acetoxy-1-naphthaldehyde, 2-acetoxybenzaldehyde, and 2-acetoxytrifluoroacetophenone with formation of carbinolamines, followed rapidly by solvent dependent *O*- or *N*-acyl transfer or dehydration.

Sir: We wish to report unusual, rapid intramolecular acyl transfer reactions via seven-ring intermediates, which represent the first step toward the development of a new class of peptide coupling reagent, as well as progress toward mimicking biochemical acyl transfer processes.

When 8-acetoxy-1-naphthaldehyde[1] (**1**) is treated with benzylamine (3 equiv, 1.2 *M*) in DMSO[2] a 70% yield of *N*-benzylacetamide is formed, together with 30% acetate ion; at 25° the half time is <1 min. We interpret this reaction as occurring via rapid formation of a carbinolamine, **2**,[3] followed by seven-ring intramolecular *N*- (path 1, amide formation) or *O*- (path 2, acetate ion formation) acyl transfer.



The product composition is strikingly solvent dependent, although in no instance could a single product be obtained. DMSO or DMF give 60–70% amide (path 1) and ~30% acetate (path 2); in 1:1 DMSO–water the ratio is 3:7, while in 1:4 acetonitrile–water, the ratio is 1:9. In other solvents dehydration of **2** to an acetoxy Schiff base (path 3) was observed. Thus in acetonitrile the ratio of products from paths 1 and 3 is 1:1; in benzene, carbon tetrachloride, or chloroform no amide is formed, and paths 2 and 3 contribute in respective ratios of 7:3, 7:3, and 1:4. Variation of the equilibrium between **2** and its zwitterion and chloroform catalysis of dehydration of **2** are presumably responsible for these results. Rate constants for the combined acyl transfer processes in acetonitrile, DMF, and 1:4 acetonitrile–water at 30° are 0.1, 0.2, and 15 M^{-1} sec^{-1}, respectively. The latter is one of the faster intramolecular acyl transfers reported for a model system.[4]

Though exact models are problematic, an estimate of the rate of intermolecular attack of amine on the acyl site of **1** is 1×10^{-3} M^{-1} sec^{-1}, observed for reaction of benzylamine and 8-acetoxy-1-nitronaphthalene[5] in acetonitrile at 30°. We note that the rapid formation of acetic acid and the Schiff base of 8-hydroxy-1-naphthaldehyde in anhydrous solvents is only consistent with intermediacy of **2** and its decomposition by path 2.

Marked changes in product composition also result with change of amine. Reaction of **1** with methyl alaninate or other substituted peptide amines yields only the product of path 3. This result excludes exploitation of derivatives of **1** in peptide synthesis.

It was hoped that the formyl group of an 8-acyloxy-1-naphthaldehyde could be protected as an acetal, and the resulting functionality employed in peptide synthesis as a C-terminal protective group[6] capable of activation under midly acidic conditions. Along with the virtues of latent activation, amide formation by amine capture and intramolecular acylation offers several intrinsic advantages over intermolecular acylation. (1) The ester function can hopefully be of a low degree of activation, minimizing side reactions.[7] (2) The amide forming step must follow first- rather than second-order kinetics. (3) Provided that the amine capture step is rate determining, the rate of amide forma-