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Solid-Phase Synthesis of Photochromic Spiropyrans

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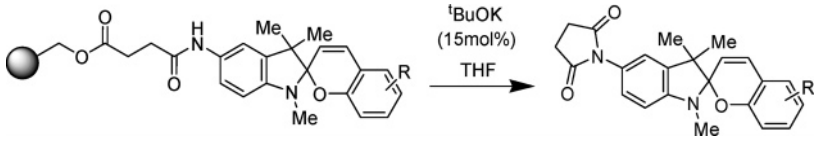
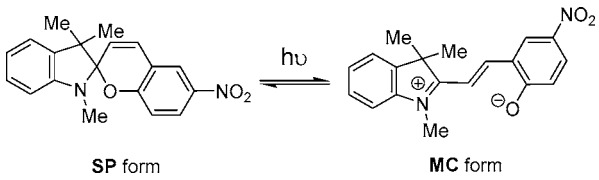
ABSTRACT



A convenient solid-phase synthesis of spiropyrans is described. A succinate linker was employed, which allows base-catalyzed cleavage of the desired photochromophore derivatized with a succinimide. Excellent yields and purities were obtained for the compounds that comprise a library of 23 spiropyrans. Opening of the succinimide ring in spiropyran could be realized under mild conditions.

The ability of photochromic molecules to undergo reversible color change upon absorption of light has led to intense investigations, resulting in the synthesis of a variety of structural motifs.[1−4] The potential applications for these molecules in the marketplace are numerous including information storage, imaging devices, smart windows, ophthalmic lenses, solar protection lenses, filters, and decorative objects.[1] Photochromic materials have also been used for photoswitching of protein activity.[5]

In the past few years, solid-phase synthesis of small organic molecules has emerged as an important tool in discovery.[6−10] Its use can avoid extensive workup, recrystallization, and chromatographic purification of the product. It also allows for easy automation of the synthesis process and convenient handling of polar molecules throughout the synthetic protocol. Moreover, difficult or slow reactions can be facilitated by use of excess of reagents without any added complications in the ultimate purification step. The application of solid-phase synthesis methods to the preparation of photofunctional materials, such as photochromic spiropyran dyes, introduces some unique challenges. Spiropyrans typically can exist as an equilibrium mixture between spiropyran (SP) and the colored forms of merocyanines (MC) which themselves can comprise mixtures of geometric isomers with a range of differential stabilities and reactivity (eq 1).[2]



(1)

The development of methods for the synthesis of a library of photochromic spiropyran compounds could facilitate the

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(2) Bertelson, R. C. *Organic Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R., Eds.; Plenum Press: New York, 1999; pp 1−83.

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(4) Guglielmetti, R. In *Photochromism: Molecules and Systems*; Durr, H., Bouas-laurent, H., Eds.; Elsevier: Amsterdam, 1990; pp 314−466. Spiropyrans, especially indolinospiropyrans, have been extensively studied. Although a large number of them have been synthesized, there is no good correlation between the structures and their photochromic properties such as thermal stability, fatigue resistance, and photosensitivity; thus, prediction of photochromic behavior is often risky.

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generation of diverse photochromic spiropyrans and ultimately lead to the identification of structures with improved photophysical properties. In this paper, we document a protocol for the convenient synthesis of a small library of photochromic spiropyrans on solid phase; such strategies for this class of materials until now have remained unexplored.

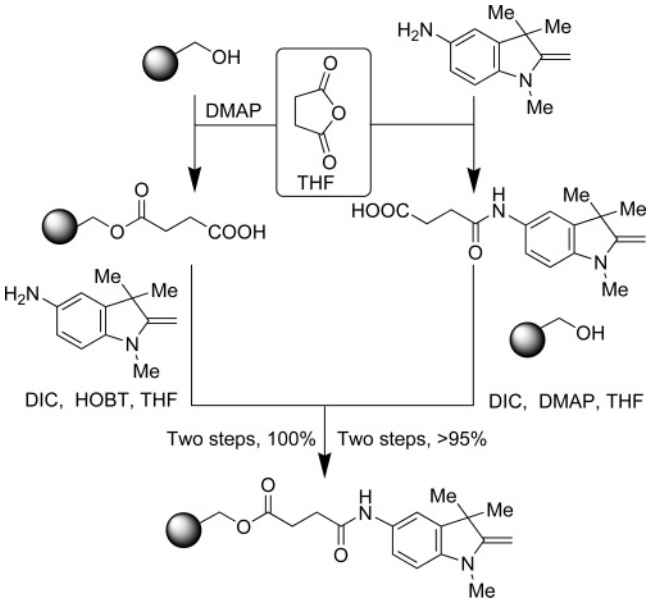
The most common photochromic spiropyran scaffold is generally prepared by condensation of indoline (Fischer's base) with an equal amount of a substituted salicylaldehyde in ethanol or toluene. This well-studied process is not without some well-known problems:[4] (1) the formation of byproducts, in particular those resulting from the condensation of two molecules of indoline with one molecule of the salicylaldehyde; (2) when yield in the condensation reaction is low the desired spiropyrans are recalcitrant to crystallize, which is crucial for purification, as (3) purification by silica gel chromatography leads to significant yield loss because of the tendency of the photochromic spiropyrans to isomerize to the more polar merocyanines on silica gel or alumina. Moreover, spiropyrans obtained from chromatography purification techniques are not suitable for fluorescent spectroscopic studies because exposure to silica gel can also catalyze the formation of colored fluorescent impurities.[3]

We surmised that in addition to bypassing the problems outlined above the use of a solid-phase synthesis approach would have the added advantage that there are numerous indolines and salicylaldehydes that can be accessed from commercial sources or through straightforward synthesis.[6−10] However, the handling of photochromic compounds is complicated by the fact that they can consist of a mixture of isomeric structures, such as spiropyrans and merocyanines. In this regard, it is known that in the presence of acid, spiropyran opening can occur, leading to the formation of merocyanines which can undergo reaction with nucleophiles.[11] Thus, any solid-phase synthesis approach would demand judicious choice of linking and release strategies.

In our investigations, we selected the easily available 5-amino-1,3,3-trimethylindoline as our key starting material.[12] The amine group present in the indoline would permit subsequent derivatization of the products from the solid-phase library synthesis approach. In our initial attempt, the 5-amino-1,3,3-trimethyl indoline was directly linked to polystyrene-COCl using triethylamine and DMAP. The reaction of the bound indoline with salicylaldehydes resulted in significant coloration of the bead (from colorless to blue-black), and no trace of desired spiropyrans could be obtained after treatment with acid or base in attempts to effect release.[13]

We subsequently found that indoline could be immobilized successfully onto Wang resin via a succinate linker following two efficient strategies (Scheme 1). In the first of these,

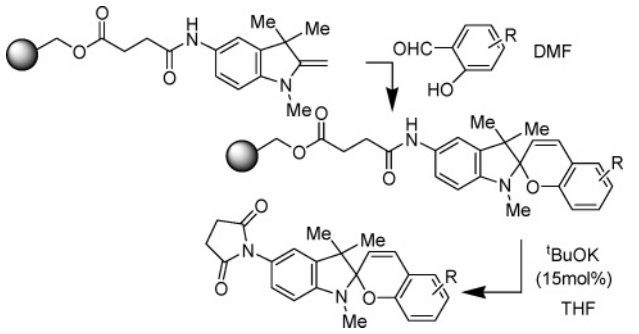
Scheme 1. Synthesis of Solid-Supported Indoline



succinic anhydride is allowed to react with Wang resin and the ensuing acid coupled with the 5-aminoindoline (DIC, HOBT). Alternatively, the succinic anhydride can be first coupled to the 5-aminoindoline and the resulting carboxylic acid attached onto the Wang resin (DIC, DMAP). Both of these approaches afforded excellent yields of the desired, bound solid-supported indoline.[14]

The polymer-bound indoline was then allowed to react with various commercially available salicylaldehydes in DMF to generate a library of resin-bound spiropyrans (See Scheme 2). Following successful formation of the spiropyran,

Scheme 2. SPOS Synthesis of Spiropyran Library



various alkaline conditions were then examined to effect release of the desired product from the solid support. The

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(11) For salt formation of merocyanines, see, for example: (a) Giordani, S.; Gejas, M. A.; Raymo, R. M. *Tetrahedron* **2004**, *60*, 10973. (b) Raymo, R. M.; Giordani, S. *J. Am Chem. Soc.* **2001**, *123*, 4651. (c) Zhou, J.; Li, Y.; Tang, Y.; Zhao, F.; Song, X.; Li, E. *J. Photochem. Photobiol. A: Chem.* **1995**, *90*, 117. (d) Sun, X.; Fan, M.; Meng, J.; Knobbe, E. T. *J. Photochem. Photobiol. A: Chem.* **1997**, *102*, 213. (e) Shiozaki, H. *Dyes Pigm.* **1997**, *33*, 229.

(12) Gale, D. J.; Wilshire, J. F. K. *J. Soc. Dyers Colour* **1974**, *90*, 97.

(13) The negative photochromism of amino spiropyran has been noticed by: (a) Guglielmetti, R. In *Photochromism: Molecules and Systems*; Durr, H., Bouas-laurent, H., Eds.; Elsevier: Amsterdam, 1990; p 323. (b) Ratner, J.; Kahana, N.; Warshawsky, A.; Krongauz, V. *Ind. Eng. Chem. Res.* **1996**, *35*, 1307.

(14) The progress of the coupling reaction could be monitored by IR (KBr) spectroscopy. Yan, B. *Acc. Chem. Res.* **1998**, *31*, 621.

use of excess amounts of strong bases such as KOH or ^{t}BuOK in THF led to partial conversion to afford mixtures of 5′-succinimidospiropyran and its hydrolyzed form within 20 min; however, longer treatment led to significant decomposition. When weaker bases such as diisopropylamine and piperidine were used, the rate of release of spiropyran was extremely slow and incomplete, even after extended time and repeated treatments. 1,8-Diazabicyclo[5,4,0]undec-7-ene (DBU) in THF was found to be effective; however, the process or complete release required over 16 h, and repeated treatments were required. After additional investigations, the optimal condition for clean release was identified to be treatment of the solid-phase bound spiropyaran with catalytic amount of ^{t}BuOK in THF (0.1 M), whereupon clean release could be realized in 20 min. The cyclization−release methodology also provides a convenient way to calculate the loading of starting indoline onto the resin. Direct cleavage of a weighed quantity of resin loaded with indoline with ^{t}BuOK in THF gave material that could be analyzed by ^{1}H NMR spectroscopy ($CDCl_3$) using hexamethyldisiloxane (HMDSO) as internal standard.[15] Using either of two methods of attachment, loading of indoline was found to be over 95%.

A library consisting of 23 spiropyrans was synthesized following the protocol delineated above, and the yields and purities that were observed are collected in Table 1. Even quite

Table 1. Spiropyran Library by Solid-Phase Synthesis

entry	R	R′	yield[a] (%)	purity[b] (%)
1	H	H	quant	96.4
2	6-Br	H	quant	93.9
3	6-Cl	H	quant	96.7
4	6-F	H	quant	97.6
5	6-NO_2	H	quant	96.6
6	6-Cl	8-Cl	quant	95.9
7	6-Br	8-Br	quant	97.1
8	8-I	8-I	99.5	97.7
9	6-Br	8-MeO	98.5	93.7
10	8-CHO	6-Me	98.8	94.8
11	8-OH	H	quant	*c*
12	6-Me	H	95.9	95.4
13	8-Me	H	quant	95.6
14	6-MeO	H	82.1	95.4
15	8-EtO	H	98.6	95.0
16	8-MeO	H	99.5	96.3
17	6-OH	H	quant	*c*
18	6-^{t}Bu	H	89.4	92.7
19	8-^{t}Bu	H	97.7	95.6
20	6-^{t}Bu	8-^{t}Bu	quant	93.6
21	7-MeO	H	82.1	*c*
22	5-MeO	7-MeO	82.9	95.7
23	8-MeO	6-NO_2	quant[d]	*c*

[a] The yield of crude spiropyran is based on theoretical loading of the Wang resin; [b] The purity was determined by HPLC; [c] The purity could not be determined by HPLC due to tautermerization of SP and MC, however ^{1}H NMR indicated good purity of SP (see the Supporting Information); [d] The product was released by DBU.

hindered or very inactive salicylaldehydes can generate the products in good to excellent yield and excellent purity. A typical ^{1}H NMR spectra of crude product and purified spiropyran are shown in Figure 1. In one case (entry 23) wherein

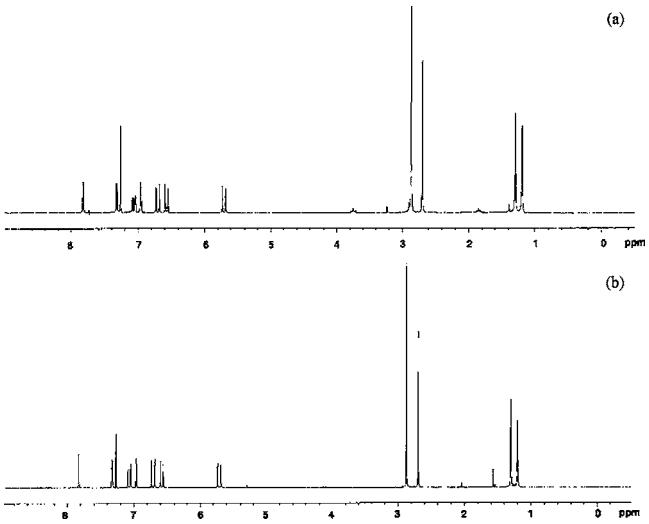


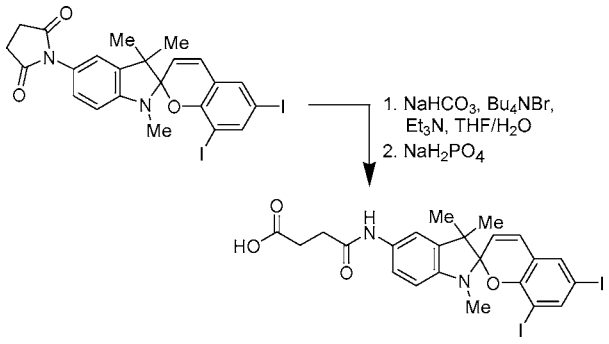
Figure 1. ^{1}H NMR of 6,8-diiodo-5′-succinimido-1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2′-indoline] in $CDCl_3$ (300 MHz): (a) crude product, (b) purified.

certain amount of MC coexisted with SP in solution 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) was discovered to be effective for release.

The method we have described is also suitable for the synthesis of preparative quantities of spiropyrans for testing through the use of high-loading Wang resin. For example, 6-nitro-5′-succinimido-1′,3,3′-trimethylspiro[2*H*-1-benzopyran-2,2′-indoline] (entry 5, Table 1) could be prepared with high-loading Wang resin (1.28 mmol/g) on a 100 mg scale in over 85% yield after recrystallization.

The strategy for the solid-phase synthesis of spiropyrans we have described is not traceless, as the products retain the succinimide linker. However, this can be used as a handle, which through further elaboration allows for modification of the bulk properties of the photochromic core in subsequent formulations.[16] Thus, the succinimide ring in the end product can be opened under mild conditions to generate free acid,

Scheme 3. Ring Opening of Succinimide in Spiropyran



allowing further funtionalization through the use of various coupling technologies.[3] For example, 5′-carboxypropionylamino-6,8-diiodo-1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2′-indoline] could be prepared in 74% yield (see Scheme 3).

In conclusion, we have for the first time demonstrated a convenient solid phase synthesis approach to novel spiropyrans through the use of a succinate linker utilizing commercially available, inexpensive starting materials. Additional studies are envisioned, which will lead to larger libraries possessing diversely functionlized photochromic spiropyrans. These results will be reported as they become available.

Acknowledgment. We thank the ETH for an internal research grant (TH-Gesuch).

Supporting Information Available: General procedure for solid-phase synthesis, crude ^{1}H NMR spectra, and HPLC spectra of spiropyrans, as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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