An Innovative and Atom-Efficient Synthesis of Bioactive 2-Aroylfuran Derivatives Using Macroporous Polymer-Supported Cyanide

Arash Mouradzadegun,* Fatemeh Abadast

Department of Chemistry, Faculty of Science, Shahid Chamran University, Ahvaz, Iran
Fax +98(611)3337009; E-mail: arash_m@scu.ac.ir

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Abstract: A novel and safe approach was developed for the synthesis of bioactive 2-aroyl-3,5-diarylfurans in excellent yields by using a cyanide-impregnated anion-exchange resin as a versatile reagent. The possibility of reusing the polymer-supported reagent makes the process environmentally friendly and economically advantageous.

Key words: furans, green chemistry, ring contraction, heterocycles, nucleophilic additions

A key principle of green chemistry is to design new synthetic procedures that eliminate the generation of waste and that avoid the use of toxic and hazardous reagents, thereby reducing costs and developing environmentally benign processes.[1] The concept of atom-efficiency in green chemistry focuses on the reduction or, preferably, the elimination of byproduct formation.[2] Polymer-supported reagents[3] have a significant role in green chemistry, as the use of such reagents provides a practical method for cleaner preparation and more efficient purification of target molecules.[4]

Substituted furans are an intriguing class of heterocycles that exhibit a wide range of biological activities[5] and appear as key structural units in many important pharmaceuticals, natural products, and other materials.[6] Among this family of compounds, 2-aroylfuran derivatives have attracted attention because they represent the core units of many naturally occurring compounds, for example, the two enantiomers of frontalin,[7] a bark beetle pheromone that has useful control activities against harmful insect infestations.[7,8] Some 2-aroylfuran derivatives have tuberculostatic activities,[9] and other derivatives have been employed as intermediates for the synthesis of targets that possesses fungicidal and medicinal activities.[10,11]

Generally, 2-aroylfuran derivatives are synthesized by the reaction of pyrylium salts with O-nucleophiles in the presence of a base and iodine.[10,12] However, this reaction has several drawbacks, such as the need for extended reaction times (e.g., 18 h for pyrylium salt **1a**), poor yields, and complicated and often laborious workup and purification steps, all of which render the approach unsatisfactory from the standpoint of atom-efficiency.

With this background and as part of our continuing efforts to develop efficient and environmentally friendly transformations[13] and to apply them to the synthesis of biologically important molecules,[14] we developed a highly practical, straightforward, and green approach to the synthesis of bioactive 2-aroylfuran derivatives by ring contraction of pyrylium salts in the presence of a cyanide-exchanged macroporous polymer resin.

We recently investigated the reaction of pyrylium salts with sodium cyanide in boiling acetonitrile, and we obtained substituted 2-furyl acetonitriles **4** within a short time as the sole products (Scheme 1).[14] Surprisingly, allowing the same reaction to run for a prolonged period led to the formation of a new compound, the corresponding 2-aroylfuran **7**, along with the development of an intensely red solution. The formation of 2-aroylfurans **7** is of considerable interest, because this is the first report of the synthesis of these useful compounds by ring contraction of a pyrylium salt, involving a carbon nucleophile instead of the usual oxygen nucleophiles. This unexpected result encouraged us to optimize the conditions for the synthesis of 2-aroylfurans.

Initially, we chose 2,4,6-triphenylpyrylium perchlorate as a model compound and we examined the effect of the solvent. Among ethanol, acetonitrile, dichloromethane, and tetrahydrofuran, acetonitrile gave the best results. Next, we screened the effect of changing the ratio of the reagents and substrates for the reaction, and the best yield was obtained by using a reagent-to-substrate ratio of 1:4.

We then examined the scope and generality of our new ring contraction by using various triarylpyrylium perchlorates under our optimized reaction conditions.[15] The structures of resulting 2-aroyl-3,5-diarylfurans **7a**–**f** were established unambiguously by physical and spectroscopic (IR, ^{1}H NMR, and ^{13}C NMR) analyses (see the Supporting Information). A mechanistic rationale with a possible sequence of events is shown in Scheme 1.

The first step of the reaction gives the α-cyanopyran **2**, which undergoes electrocyclic ring opening to form the acyclic valence tautomer **3**. The thermally unstable cyanodienone **3** then undergoes rapid cyclization to the 2-furyl acetonitrile **4**. Subsequent hydrolysis of the cyano group followed by elimination of carbon dioxide gives the 2-aroylfuran **7**. Nucleophilic attack by hydroxyl ions on the carbonyl moiety of dienone **5** gives anion **6**, which transforms into **7** by sequential nucleophilic ring closure and oxidative aromatization. The fact that the 2-furyl acetonitrile **4** can be isolated after a short reaction time suggests that the activation energy for the forward reaction of com-

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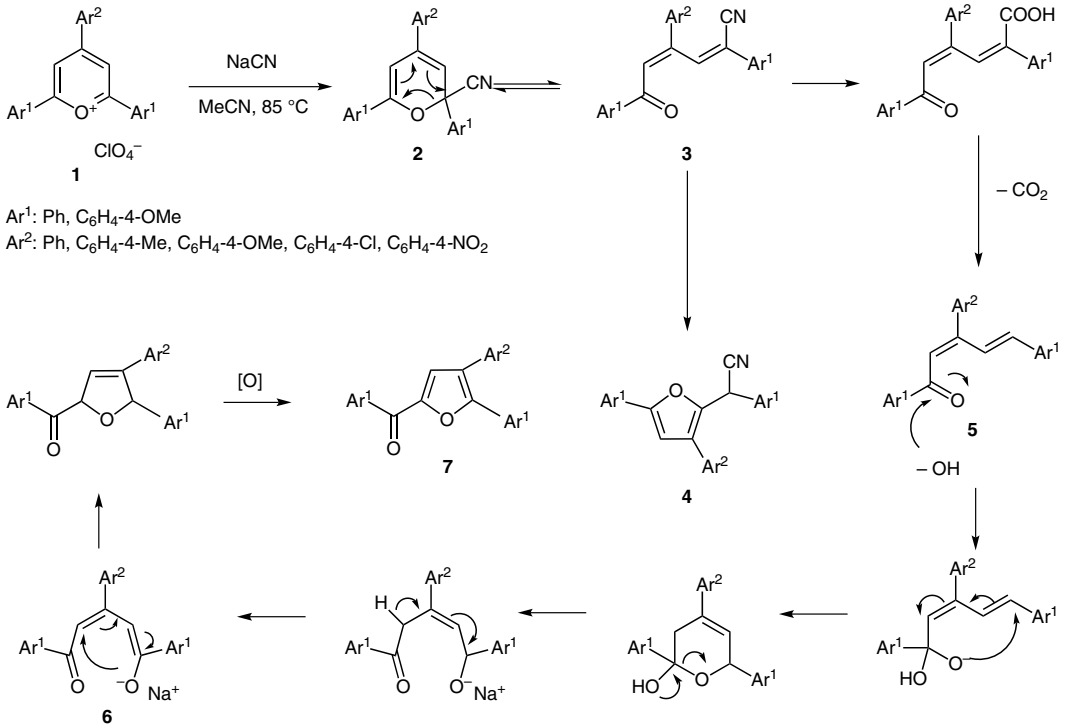


Scheme 1 Plausible mechanism for the formation of 2-aroylfuran derivatives **7**

pound **4** is lower than that for the 2-aroylfuran **7** (see the Supporting Information).

We carried out further experiments to support our proposed mechanism. The isolated cyanodienone intermediate **3**, which we characterized by physical and spectroscopic analysis (Supporting Information), was found to afford product **7** on prolonged heating. Furthermore, prolonged heating of 2-furyl acetonitrile **4** in acetonitrile also resulted in the formation of compound **7**, along with a small amount of compound **3**, in agreement with our proposed mechanism.

The formation of a deep-red coloration during reaction can be ascribed to the formation of the anion **6**, typical of species generated in the presence of O-nucleophiles. The formation of the anion **6** as a byproduct is one of the major drawbacks for the synthesis of 2-aroyl-3,5-diarylfurans **7** by standard methods, as this side reaction reduces the yield of the desired product[10,12] (see Supporting Information).

This development prompted us to search for a synthetic route to **7** that would avoid any appreciable concentration of byproduct **6** in solution and that would remove the need to use free inorganic cyanide. The fact that perchlorate ions bind more strongly to basic anion-exchange resins than does cyanide ion,[16] coupled with the well-known high reactivity of pyrylium salts in addition reactions, suggested that we ought to examine the reaction of pyrylium perchlorates with the cyanide form of a porous anion-exchange polymer.

The cyanide-supported resin was prepared by treating the chloride form of Amberlite IRA 910 (a macroporous resin containing quaternary ammonium groups) with aqueous sodium cyanide.[17] The typical loading of the cyanide anion on the support was 1.4 mmol·g^{-1}, as determined by potentiometry.[18]

When we treated the model substrate triphenylpyrylium perchlorate (**1a**) with the cyanide-containing resin, we obtained (3,5-diphenyl-2-furyl)(phenyl)methanone (**7a**) in excellent yield. As shown in Figure 1, none of the red-colored byproduct **6** was formed. A weak interaction between anion **6** and the resin, which increases the nucleophilicity of the anion, might contribute to the suppression of byproduct formation and to the rapid progress of the reaction. In addition, the high porosity of the resin appears to allow good diffusion of reactants and solvents into the interior of the polymer matrix.

Figure 1 Synthesis of 2-aroyl-3,5-diarylfuran **7** using sodium cyanide (right) and cyanide-containing resin (left)

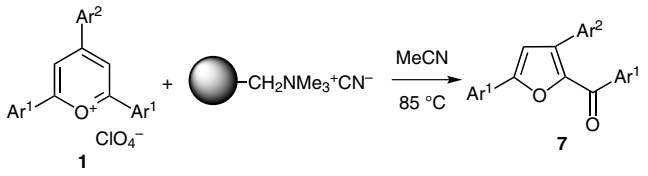
The product can be isolated by filtering off the resin and purified by removing the solvent under reduced pressure without laborious aqueous workup or chromatographic purification steps.

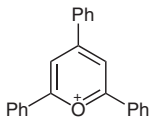
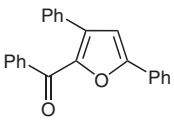
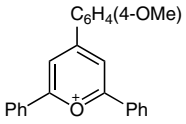
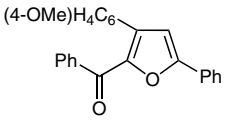
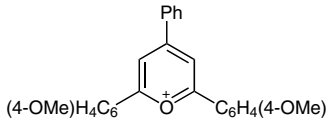
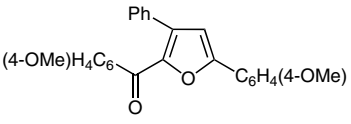
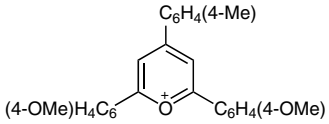
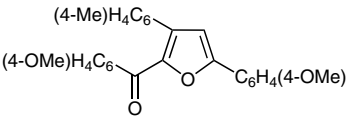
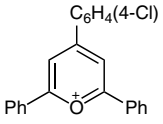
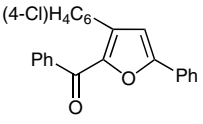
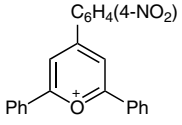
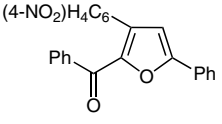
To test the scope and utility of our synthetic protocol, we examined the process with a range of triarylpyrylium perchlorates containing electron-donating or electron-withdrawing groups at the *para*-position of the substituted phenyl rings in the presence of the cyanide-impregnated anion-exchange resin.[19] Representative results of this synthetic modification are listed in Table 1. Electron-donating substituent decreased the reaction rate (entries 1–4), possibly because these groups decrease the positive charge at the α-position of the heterocyclic ring. The presence of more strongly electron-donating groups led to longer reaction times. In contrast, the presence of an electron-withdrawing group (entries 5 and 6) accelerated the reaction.

This protocol therefore offers the possibility of considerably decreasing the reaction time and improving the yield in comparison with conventional conditions. Furthermore, the procedure gives the desired 2-aroylfuran derivatives **7** exclusively with none of the corresponding byproducts **6**. In addition, the resin-supported cyanide is much less hazardous to use, because the cyanide residues are retained on the Amberlite resin and are not extracted into either aqueous or organic media. These aspects point to this being an atom-efficient process that produces less waste than would otherwise have arisen from the use of excess reagents.

In conclusion, a cyanide-containing resin was successfully used in a high-yielding and clean conversion of a range of triarylpyrylium perchlorates into 2-aroylfuran derivatives. Because of its operational simplicity, this effective synthetic route minimizes environmental impact in many ways, including ease of manipulation and workup, better control of hazardous cyanide, shorter reaction times, and minimization of byproducts. We expect that this green and practical protocol will be useful in academic research and in pharmaceutical development.

Table 1 Conversion of Various Triarylpyrylium Salts **1** into the Corresponding 2-Aroyl-3,5-diarylfurans **7** at 85 °C by Using Cyanide-Containing Resin



Entry	Substrate (**1**)	Product (**7**)	Time (h)	Yield (%)
1			7	86
2			8	87
3			10	87
4			11	91
5			5	86
6			4	84

Acknowledgments

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, **1998**. (b) *Benign by Design: Alternative Synthetic Design for Pollution Prevention, ACS Symposium Series 577*; Anastas, P. T.; Farris, C. A., Eds.; American Chemical Society: Washington DC, **1994**. (c) Sheldon, R. In *Green Chemistry in the Pharmaceutical Industry*; Dunn, P. J.; Wells, A. S.; Williams, M. T., Eds.; Wiley-VCH: Weinheim, **2010**, Chap. 1 1. (d) Hafez, E. A. A.; Al-Mousawi, S. M.; Moustafa, M. Sh.; Sadek, K. U.; Elnagdi, M. H. *Green Chem. Lett. Rev.* **2013**, *6*, 189. (e) Shen, S.-C.; Sun, X.-W.; Lin, G.-Q. *Green Chem.* **2013**, *15*, 896. (f) Green, G. M.; Peet, N. P.; Metz, W. A. *J. Org. Chem.* **2001**, *66*, 2509.

(2) (a) Halland, N. *Synlett* **2012**, *23*, 2969. (b) Sinnwell, S.; Inglis, A. J.; Davis, T. P.; Stenzel, M. H.; Barner-Kowollik, C. *Chem. Commun.* **2008**, 2052. (c) Nagano, Y.; Orita, A.; Otera, J. *Adv. Synth. Catal.* **2003**, *345*, 643. (d) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233. (e) Rao, M. L. N.; Banerjee, D.; Dhanorkar, R. J. *Synlett* **2011**, 1324. (f) Zangade, S. B.; Mokle, S. S.; Shinde, A. T.; Vibhute, Y. B. *Green Chem. Lett. Rev.* **2013**, *6*, 123. (g) Murai, M.; Yoshida, S.; Miki, K.; Ohe, K. *Chem. Commun.* **2010**, *46*, 3366. (h) Ananikov, V. P.; Kashin, A. S.; Hazipov, O. V.; Beletskaya, I. P.; Starikova, Z. A. *Synlett* **2011**, 2021. (i) Lange, J. H. M.; Verhoog, S.; Sanders, H. J.; Loevezijn, A. V.; Kruse, C. G. *Tetrahedron Lett.* **2011**, *52*, 3198. (j) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437. (k) Williams, D. B. G.; Lawton, M. C. *Green Chem.* **2008**, *10*, 914. (l) Rao, M. L. N.; Awasthi, D. K.; Talode, J. B. *Synlett* **2012**, *23*, 1907.

(3) (a) Dockx, J. *Synthesis* **1973**, 441. (b) Chesney, A. *Green Chem.* **1999**, *1*, 209. (c) Harland, C. E. *Ion Exchange: Theory and Practice*; Royal Society of Chemistry: Cambridge, **1994**, Chap. 5. (d) Vernon, F. *Sel. Annu. Rev. Anal. Sci.* **1972**, 83. (e) Toy, P. H.; Shi, M. *Tetrahedron* **2005**, *61*, 12025.

(4) (a) Tang, E.; Chen, B.; Zhang, L.; Li, W.; Lin, J. *Synlett* **2011**, 707. (b) Tamami, B.; Iranpoor, N.; Rezaei, R. *Synth. Commun.* **2003**, *33*, 3153. (c) Dare, E. O.; Liu, L.-K.; Peng, J. *Dalton Trans.* **2006**, 3668. (d) Alcalde, E.; Dinarès, I.; Ibáñez, A.; Mesquida, N. *Chem. Commun.* **2011**, *47*, 3266. (e) Verdié, P.; Ronga, L.; Cristau, M.; Amblard, M.; Cantel, S.; Enjalbal, C.; Puget, K.; Martinez, J.; Subra, G. *Synfacts* **2011**, 1382. (f) Solabannavar, S. B.; Desai, U. V.; Mane, R. B. *Green Chem.* **2002**, *4*, 347. (g) Sheng, S.-R.; Liu, X.-L.; Wang, X.-C.; Xin, Q.; Song, C.-S. *Synthesis* **2004**, 2833.

(5) (a) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Vol. 4; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 657. (b) Barancelli, D. A.; Mantovani, A. C.; Jesse, C.; Nogueira, C. W.; Zeni, G. *J. Nat. Prod.* **2009**, *72*, 857. (c) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076. (d) Cho, C.-H.; Shi, F.; Jung, D.-I.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2012**, *14*, 403. (e) Chen, K.-W.; Syu, S.; Jang, Y.-J.; Lin, W. *Org. Biomol. Chem.* **2011**, *9*, 2098. (f) Reichstein, A.; Vortherms, S.; Bannwitz, S.; Tentrop, J.; Prinz, H.; Müller, K. *J. Med. Chem.* **2012**, *55*, 7273.

(6) (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (b) Ji, W.-h.; Pan, Y.-m.; Zhao, S.-y.; Zhan, Z.-p. *Synlett* **2008**, 3046. (c) Rodríguez, A.; Moran, W. J. *Tetrahedron Lett.* **2011**, *52*, 2605. (d) Piller, F. M.; Knochel, P. *Synthesis* **2011**, 1751. (e) Yu, C.; Lu, J.; Li, T.; Wang, D.; Qin, B.; Zhang, H.; Yao, C. *Synlett* **2011**, 2420. (f) Hou, X. L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2003**, *15*, 167. (g) Sniady, A.; Durham, A.; Morreale, M. S.; Marcinek, A.; Szafert, S.; Lis, T.; Brzezinska, K. R.; Iwasaki, T.; Ohshima, T.; Mashima, K.; Dembinski, R. *Synfacts* **2008**, 1084.

(7) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synthesis* **1997**, 509.

(8) (a) Kinzer, G. W.; Fentiman, A. I. Jr.; Page, T. F.; Faltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature* **1969**, *221*, 477. (b) Silverstein, R. M. *Science* **1981**, *213*, 1326. (c) Oehlschlager, A. C.; Johnston, B. D. *J. Org. Chem.* **1987**, *52*, 940. (d) Singh, S.; Guiry, P. J. *J. Org. Chem.* **2009**, *74*, 5758.

(9) Lutz, R. E.; Reveley, W. G. *J. Am. Chem. Soc.* **1941**, *63*, 3178.

(10) Bello, A. M.; Kotra, L. P. *Tetrahedron Lett.* **2003**, *44*, 9271.

(11) (a) Francesconi, I.; Wilson, W. D.; Tanious, F. A.; Hall, J. E.; Bender, B. C.; Tidwell, R. R.; McCurdy, D.; Boykin, D. W. *J. Med. Chem.* **1999**, *42*, 2260. (b) Brown, C. D.; Chong, J. M.; Shen, L. *Tetrahedron* **1999**, *55*, 14233. (c) Mortensen, D. S.; Rodriguez, A. L.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2521. (d) Jiang, S.; Tala, S. R.; Lu, H.; Abo-Dya, N. E.; Avan, I.; Gyanda, K.; Lu, L.; Katritzky, A. R.; Debnath, A. K. *J. Med. Chem.* **2011**, *54*, 572.

(12) (a) Pedersen, C. L. *Acta Chem. Scand., Ser. B* **1975**, *29*, 791. (b) Francesconi, I.; Patel, A.; Boykin, D. W. *Synthesis* **1999**, 61.

(13) (a) Mouradzadegun, A.; Gheitasvand, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1385. (b) Ganjali, M. R.; Norouzi, P.; Emami, M.; Golmohamadi, M.; Pirelahi, H.; Mouradzadegun, A. *J. Chin. Chem. Soc (Weinheim, Ger.)* **2006**, *53*, 1209. (c) Mouradzadegun, A.; Pirelahi, H. *J. Photochem. Photobiol., A* **2001**, *138*, 203. (d) Mouradzadegun, A.; Dianat, Sh. *J. Heterocycl. Chem.* **2009**, *46*, 778. (e) Mouradzadegun, A.; Ghasem Hezave, F.; Karimnia, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 84. (f) Mouradzadegun, A.; Abadast, F. *Monatsh. Chem.* **2013**, *144*, 375. (g) Kiasat, A. R.; Mouradzadegun, A.; Elahi, S.; Fallah-Mehrjardi, M. *Chin. Chem. Lett.* **2010**, *21*, 146. (h) Mouradzadegun, A.; Kiasat, A. R.; Kazemian Fard, P. *Catal. Commun.* **2012**, *29*, 1.

(14) Mouradzadegun, A.; Abadast, F. *Tetrahedron Lett.* **2013**, *54*, 2641.

(15) **Reaction of Triarylpyrylium Perchlorates 1 with Sodium Cyanide; General Procedure**
CAUTION: *Cyanide salts can be absorbed through the skin and are extremely toxic*.
The appropriate triarylpyrylium perchlorate (1 mmol) was dissolved in MeCN (10 mL), NaCN (4 mmol) was added, and the mixture was refluxed until the reaction was complete. The solvent was then evaporated under vacuum, and the residue was adsorbed onto silica gel, which was mounted on a silica gel column and eluted with 20:80 Et_2O–hexane. The purified product was crystallized from EtOH.

(16) (a) Kitchener, J. A. In *Ion Exchangers in Organic and Biochemistry*; Calmon, C.; Kressman, T. R. E., Eds.; Interscience: New York, **1957**. (b) Harland, C. E. *Ion*

Exchange: Theory and Practice, 2nd ed.; Royal Society of Chemistry: Cambridge, **1994**, 90.

(17) **Polymer-Supported Cyanide Anion**
Amberlite IRA 910 (chloride ion form) was washed several times with distilled H_2O to remove foreign material. The dried resin (100 g) was then stirred with a soln of NaCN (32 g) in H_2O (450 mL) for 12 h. The cyanide solution was decanted, and the resin was washed with distilled H_2O until the washings gave a negative cyanide test ($AgNO_3$). The water was then decanted and replaced by the solvent to be employed as the reaction medium.

(18) **Estimation of the Capacity of the Polymer-Supported Cyanide**
A sample of resin-supported cyanide anion (1.00 g) was stirred for 12 h with KI (830 mg) in H_2O (10 mL). The resin was filtered off and washed several times with distilled H_2O. The combined filtrate and washings were titrated against 0.1 M aq $AgNO_3$ using a potentiometer. The capacity was generally found to be 1.4 mmol per gram of dry resin. Used resin could be readily regenerated by washing it sequentially with 1 M aq NaCl and aq NaCN.

(19) **Reaction of Triarylpyrylium Perchlorates 1 with Cyanide-Impregnated Anion-Exchange Resin; General Procedure**
The appropriate triarylpyrylium salt **1** (1 mmol) was stirred with the cyanide-impregnated Amberlite IRA 910 resin (4 mmol) in refluxing MeCN (10 mL) until the reaction was complete (TLC). The resin was then removed by filtration, and the filtrate was evaporated to give a crude product that was crystallized from EtOH.

