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EXPEDITIOUS SYNTHESIS OF AROMATIC CYANODIENONES USING NEUTRAL ALUMINA AS A VERSATILE HETEROGENEOUS CATALYST

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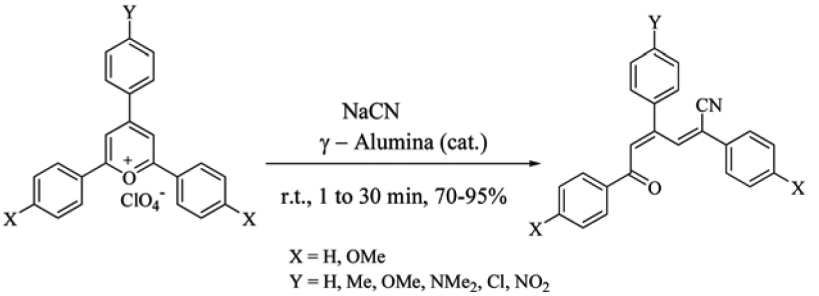
GRAPHICAL ABSTRACT



Abstract *The work described herein employs neutral alumina as an effective catalyst for ring opening of triarylpyrylium perchlorates to corresponding aromatic cyanodienones, which have main roles in biological activities. The present porous catalyst has several advantages, it is inexpensive, thermally and mechanically stable, nontoxic, and highly resistant against organic solvents. It increases the reaction rate many fold when compared with conventional reaction conditions. Moreover, the recovered alumina can be used several times without serious decrease in activity.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Aromatic cyanodienone; heterogeneous catalysis; neutral alumina; pyrylium salt

INTRODUCTION

Transition aluminas are some of the most widely used materials in heterogeneous catalysis because of several attractive features.[1] They are applied industrially as filler, absorbent, drying agent, catalyst, catalyst support, and reagent in a wide variety of chemical processes.[2] Among the transition aluminas, γ-alumina

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plays a pivotal role in the industry, with numerous applications in refining and petrochemistry.[3] Further theoretical and experimental investigations revealed that neutral alumina, unlike clays and zeolites, does not contain accessible channels or cavities; however, it shows large surface area and highly porous exteriors available to substrates. It could be most commonly utilized as a catalyst as a support for the effective synthesis of target molecules.[4]

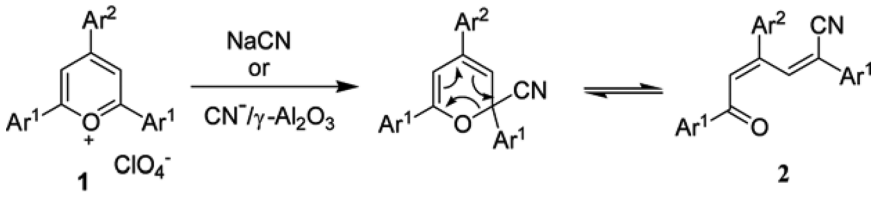
Cyanodienone derivatives, especially aromatic ones, have found use as elegant precursors to produce potent antibiotics such as butenolides,[5] which appear as a substructure in natural products, peptide analogs, and HIV-1 protease inhibitors.[6] One of the major drawbacks for the synthesis of these biologically important molecules starting from readily available triarylpyrylium perchlorates is much longer reaction time (e.g., 23 h for **1**F). Although our preceding effort in the green synthesis of these compounds using cyanide impregnated on anion exchange resin[7] decreased the reaction time to some extent, it is still a great challenge to construct these molecules using a simple cost-effective method that can be amenable to large-scale production and provide a significant tool with important implications in pharmacological industries.

In continuation to our studies on developing improved synthetic methodologies for organic transformation,[8] in the present paper, we describe a highly efficientand convenient approach toward the synthesis of aromatic cyanodienones by reaction of corresponding triarylpyrylium perchlorates with sodium cyanide using γ-alumina as common, cheap, and neutral heterogeneous catalyst.

RESULTS AND DISCUSSION

The performance of aluminas, in general, as catalyst or catalyst supports largely depends on their crystalline, textural, and chemical characteristics, as well as on their hydrothermal stabilities.[9] Empirical testing of several supports revealed that neutral alumina was most effective in activating cyanide.[10] Previous studies clearly showed that neutral alumina impregnated with cyanide ($NaCN/\gamma\text{-}A1_2O_3$) is a more efficient reagent for carrying out cyanide displacement on organic halides. The reagent affords excellent yields of the desired products but the reaction proceeds relatively slow. This was described by the fact that $NaCN/\gamma\text{-}A1_2O_3$ is uniformly distributed between active and inactive sites and that only monolayer coverage is of practical synthetic value. Moreover, the inactive cyanide was tentatively attributed to material located in small pores, inaccessible to the bulk organic phase.[11] So, to put the reactivity of impregnated cyanide ion into perspective, we have arranged the competitive and parallel analogous conversion reactions of triphenylpyrylium perchlorate as a model compound in the presence of pulverized NaCN and $CN^-/\gamma\text{-}A1_2O_3$ as reagents (Scheme 1).

First, the reaction of triarylpyrylium perchlorate with sodium cyanide was chosen as the model reaction to survey the requisite reaction condition. To know the solvent effect on the outcome of the reaction, different solvents were screened in the model reaction. It was observed that acetonitrile was the most effective solvent, furnishing the desired product in 78% yield superior to ethanol, dichloromethane, and tetrahydrofuran. Turning our attention to the molar ratio of reagent/substrate, the reaction of model compound (1 mmol) with varying amount



Ar^1 : C_6H_5, C_6H_4 *p*-OMe

Ar^2 : C_6H_5, C_6H_4 *p*-Me, C_6H_4 *p*-OMe, C_6H_4 *p*-NMe_2, C_6H_4 *p*-Cl, C_6H_4 *p*-NO_2

Scheme 1. Synthesis of aromatic cyanodienones **2** from the reaction of triarylpyrylium perchlorates **1** with NaCN and CN^-/γ-Al_2O_3.

Table 1. Trend of the model reaction with different amounts of sodium cyanide

Entry	Reagent/substrate	Time	Yield of 2 (%)
1	1	1 h	78
2	1.5	50 min	78
3	2	30 min	78
4	2.5	15 min	65

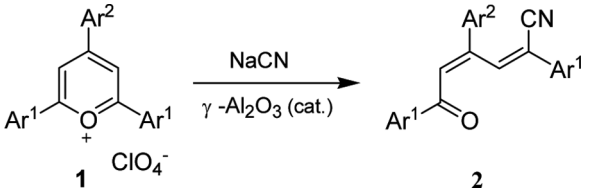
of sodium cyanide was investigated. As can be observed in Table 1, the target reaction is favored by increasing the reagent/substrate ratio as shown from the significant decrease in the reaction time. Bearing in mind that the reaction proceeds through an addition and then ring-opening mechanism, the increase in reagent concentration favors the first reaction step and, on the whole, the product formation. The decrease of the yield (65%) by employing a ratio of 2.5 (entry 4) can probably be explained by generation of other products. The best yield (78%) and the shortest time (30 min) were obtained by using the ratio reagent of substrate = 2 (entry 3). This molar ratio was considered in both cases of reagents.

Neutral alumina impregnated with cyanide was allowed to react with the model compound. Unlike other experiments,[10,11] the reaction was performed at high speed. This extraordinary result supported the assumption that perhaps besides the role of the surface area, the pore structure plays an important role in alumina activity. Therefore, we have arranged the reaction of model compound with sodium cyanide in the presence of a catalytic amount of γ-$A1_2O_3$. The reaction was successful and cyanodienone **2**A was obtained quickly with good yield. Encouraged by this

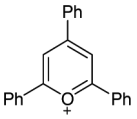
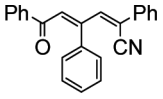
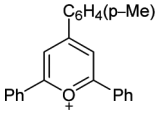
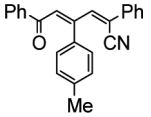
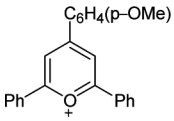
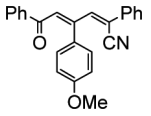
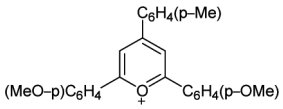
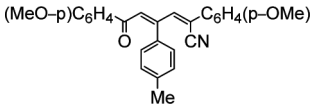
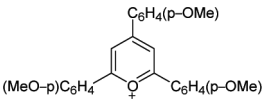
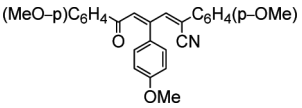
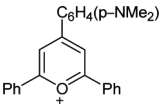
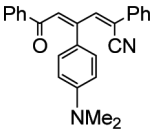
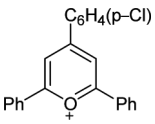
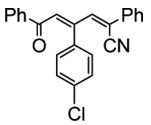
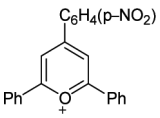
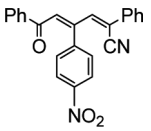
Table 2. Trend of the model reaction with different amounts of catalyst

Entry	Catalyst (mol%)	Time (min)
1	3	5
2	5	3
3	10	3

Table 3. Conversion of various triarylpyrylium salts **1** into corresponding aromatic cyanodienones **2** in acetonitrile at room temperature



1 **2**

Entry	Substrate (**1**)	Product (**2**)	Time (without catalyst)	Time (with catalyst)	Yield%
A			30 min	3 min	78
B			1 h	5 min	81
C			4 h	15 min	91
D			10 h	18 min	95
E			16 h	22 min	93
F			23 h	30 min	88
G			25 min	2 min	70
H			20 min	1 min	72

observation, further experiments were designed to survey catalytic virtue of the support in the same reaction. In this regard, the model reaction was investigated in the presence of various amounts of γ-Al_2O_3 as catalyst. As shown in Table 2, the use of as little as 3 mol% of γ-Al_2O_3 is sufficient to catalyze the reaction (entry 1).

We believed that considering the average pore diameter of γ-Al_2O_3 [40 Å (20% being >120 Å)] and the size of triphenylpyrylium perchlorate [9.5×12 Å], highly porous neutral alumina could constrain substrate or parts of it along with reactant, lower the entropy of activation of reaction, and accelerate the reaction.

To further examine the efficacy of this synthetic opportunity, the process is illustrated with various triarylpyrylium perchlorates contain electron-donating and withdrawing groups in the *para* position of substituted phenyl rings with pulverized sodium cyanide in the presence of neutral alumina (Table 3).

The data in Table 3 clearly showed that reactions of triarylpyrylium salts with sodium cyanide proceed slowly, while the presence of neutral alumina, in nearly all cases, incredibly increased the rate of reactions. The effect of substitutions was also viewed clearly in this table. The electron-donating groups cause the reactions to become slow (e.g., entries A–F). This may be explained by considering the fact that these groups decrease the positive charge on α-position of the heterocyclic ring. Stronger electron-donating groups exhibit longer reaction times. In contrast, electron-withdrawing groups (e.g., entries G and H) accelerate the reaction.

The structure of all products were settled from their physical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) data.

Furthermore, we regard the recoverability of the γ-Al_2O_3 in accordance with the heterogeneity of this system. The recovered catalyst (after washing with acetonitrile) was used in the next run with nearly consistent activity.

In summary, the superiority of using γ-Al_2O_3 over other methods includes a very rapid reaction with readily available catalyst. Further, our method can be applied to a wide range of substrates and results in good yield. Overall, the present protocol offers more efficient and particularly economically advantageous process towards the synthesis of valuable aromatic cyanodienones, which serves a useful synthetic alternative for large-scale conversions. Studies on the applications of this intriguing and cost-cutting approach in organic transformations are currently under way in our laboratory.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Monitoring of the reactions was accomplished by thin-layer chromatography (TLC). Infrared (IR) spectra were obtained on a Bomen MB:102 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra (MS) were measured on Anagilent 5975 mass spectrophotometer.

General Procedure for the Synthesis of Triarylpyrylium Perchlorates

All triarylpyrylium perchlorates were synthesized from the corresponding aldehydes and ketones by the method previously described.[12] Briefly, corresponding benzaldehyde (0.1 mol) and acetophenone (0.2 mol) were stirred at room temperature, and sulfuric acid (6 mL) was added dropwise during 30 min. The mixture was stirred at 100 °C for 60 min. Then, ethanol (200 mL) and perchloric acid 70% (10 mL) were added. The mixture was excluded to form a precipitate for 24 h. The precipitates recrystallized from acetic acid.

General Procedure for the Reaction of Triarylpyrylium Perchlorates with Sodium Cyanide

The triarylpyrylium perchlorates (1 mmol) were stirred with sodium cyanide (2 mmol) at room temperature in acetonitrile (10 mL), and the reactions were monitored by TLC using a 20:80 mixture of ether–*n*-hexane as eluent. After completion of the reaction, the solvent was evaporated under vacuum and the product **2** was worked up in aqueous ethyl acetate (to remove excess cyanide), then recrystallized from EtOH.

General Procedure for the Reaction of Triarylpyrylium Perchlorates with Cyanide Impregnated on Neutral Alumina

A 50-ml round-bottom flask was charged with 2.0 g (40.8 mmol) of sodium cyanide dissolved in 5 ml of distilled water, and then 8.0 g of γ-alumina was added. The flask was transferred to a rotary evaporator, and the water was removed under reduced pressure, keeping the bath temperature below 65 °C. Impregnated alumina was then dried (4 h, 110 °C). Then, in a round-bottomed flask, a solution of triarylpyrylium perchlorate (1 mmol) in acetonitrile (10 mL) was prepared. Cyanide impregnated on γ-alumina (2 mmol) was added and the mixture was stirred at room temperature for the appropriate time. The progress of the reaction was monitored by TLC (eluent: ether–*n*-hexane 1:4). After completion of the reaction, alumina removed by filtering, the solvent was evaporated under vacuum, and product **2** was worked up in aqueous ethyl acetate. Then the products were recrystallized from EtOH.

General Procedure for the Reaction of Triarylpyrylium Perchlorates with Sodium Cyanide in the Presence of Neutral Alumina as Catalyst

Neutral alumina (0.05 mmol) was added to a magnetically stirred mixture of the triarylpyrylium salts (1 mmol) and sodium cyanide (2 mmol) in acetonitrile (10 mL). The resulting mixture was stirred at room temperature for the appropriate time. After completion of the reaction, alumina was removed by filtering, the solvent was evaporated under vacuum, and the product **2** was worked up in aqueous ethyl acetate. Then the products were recrystallized from EtOH.

SUPPORTING INFORMATION

Full experimental detail and ^{1}H and ^{13}C NMR spectra can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENT

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REFERENCES

1. Marquez-Alvarez, C.; Zilkova, N.; Perez-Pariente, J.; Cejka, J. *Catal. Rev.-Sci. Eng.* **2008**, *50*, 222–286.
2. (a) Baumann, T. F.; Gash, A. E.; Chin, S. C.; Sawvel, A. M.; Maxwell, R. S.; Satcher Jr., J. H. *Chem. Mat.* **2005**, *17*, 395–401; (b) Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Synth. Commun.* **2008**, *38*, 4097–4106; (c) Kosydar, R.; Drelinkiewicz, A.; Lalik, E.; Gurgul, J. *Appl. Catal. A: Gen.* **2011**, *402*, 121–131; (d) Gandarias, I.; Requies, J.; Arias, P. L.; Armbruster, U.; Martin, A. *J. Catal.* **2012**, *290*, 79–89; (e) Zhang, Z.; Hicks, R. W.; Pauly, T. R.; Pinnavaia, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 1592–1593; (f) Tumma, H.; Nagaraju, N.; Reddy, K. V. *Synth. Commun.* **2010**, *40*, 1856–1866; (g) Avramescu, S. M.; Bradu, C.; Udrea, I.; Mihalache, N.; Ruta, F. *Catal. Commun.* **2008**, *9*, 2386–2391; (h) Leita, B. A.; Grayb, P.; O'Sheab, M.; Burkea, N.; Chianga, K.; Trimma, D. *Catal. Today* **2011**, *178*, 98–102.
3. (a) Cai, S.-H.; Rashkeev, S. N.; Pantelides, S. T.; Sohlberg, K. *Phys. Rev. B* **2003**, *67*, 1–10; (b) Krokidis, X.; Raybaud, P.; Gobichon, A.-E.; Rebours, B.; Euzen, P.; Toulhoat, H. *J. Phys. Chem. B* **2001**, *105*, 5121–5130; (c) Márquez-Alvarez, C.; Žilková, N.; Pérez-Pariente, J.; Čejka, J. *Catal. Rev.* **2008**, *50*, 222–286; (d) Kagyrmanova, A. P.; Chumachenko, V. A.; Korotkikh, V. N.; Kashkin, V. N.; Noskov, A. S. *Chem. Eng. J.* **2011**, *176*, 188–194.
4. (a) Ballini, R.; Bosico, G.; Fiorini, D.; Palmieri, A. *Green Chem.* **2005**, *7*, 825–827; (b) Jain, S. L.; Prasad, V. V. D. N.; Sain, B. *Catal. Commun.* **2008**, *9*, 499–503; (c) Abdollahi-Alibeik, M.; Mohammadpoor-Baltork, I.; Zolfigol, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6079–6082; (d) Hirano, M.; Yakabe, S.; Monobe, H.; Morimoto, T. *J. Chem. Res., Synop.* **1998**, 472–473; (e) Chriman, W.; Blankinship, M. J.; Taylor, B.; Harris, C. E. *Tetrahedron Lett.* **2001**, *42*, 4775–4777.
5. Balaban, A. T.; Tudose, A.; Caproiu, M. T. *Tetrahedron.* **2003**, *59*, 3291–3295.
6. (a) Harris, L. J.; Alexander, N. J.; Saparno, A.; Blackwell, B.; McCormick, S. P.; Desjardins, A. E.; Robert, L. S.; Tinker, N.; Hattori, J.; Piché, C.; Schernthaner, J. P.; Watson, R.; Ouellet, T. *Fungal Genet. Biol.* **2007**, *44*, 293–306; (b) Zhang, X.; Guo, J.; Hu, S. *Synth. Commun.* **2012**, *42*, 1551–1558; (c) Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Shinde, S. V. *Tetrahedron Lett.* **2008**, *49*, 4402–4404; (d) Sabitha, G.; Prasad, M. N.; Ramesh, M.; Yadav, J. S. *Monatsh. Chem.* **2010**, *141*, 1245–1248; (e) Fan, W. Y.; Wang, Z. L.; Zhang, Z. G.; Li, H. C.; Deng, W. P. *Tetrahedron.* **2011**, *67*, 5596–5603; (f) Clark, B.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H.; Bulheller, B.; Bringmann, G. *J. Nat. Prod.* **2005**, *68*, 1226–1230; (g) Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J.Org. Chem.* **2003**, *68*, 670–673; (h) Du, G.-F.; He, L.; Gu, C.-Z.; Dai, B. *Synth. Commun.* **2012**, *42*, 1226–1233.
7. Mouradzadegun, A.; Abadast, F. *Monatsh. Chem.* **2013**, *144*, 375–379.

8. (a) Mouradzadegun, A.; Gheitasvand, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1385–1388; (b) Ganjali, M. R.; Norouzi, P.; Emami, M.; Golmohamadi, M.; Pirelahi, H.; Mouradzadegun, A. *J. Chin. Chem. Soc.* **2006**, *53*, 1209–1214; (c) Mouradzadegun, A.; Pirelahi, H. *J. Photochem. Photobiol. A: Chem.* **2001**, *138*, 203–205; (d) Mouradzadegun, A.; Dianat, Sh. *J. Heterocycl. Chem.* **2009**, *46*, 778–781; (e) Mouradzadegun, A.; Ghasem Hezave, F.; Karimnia, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 84–87; (f) Kiasat, A. R.; Mouradzadegun, A.; Elahi, S.; Fallah-Mehrjardi, M. *Chin. Chem. Lett.* **2010**, *21*, 146–150; (g) Mouradzadegun, A.; Kiasat, A. R.; KazemianFard, P. *Catal. Commun.* **2012**, *29*, 1–5; (h) Mouradzadegun, A.; Abadast, F. *Tetrahedron Lett.* **2013**, *54*, 2641–2644.
9. Sun, Z.-X.; Zheng, T.-T.; Bo, Q.-B.; Du, M.; Forsling, W. *J. Colloid Interface Sci.* **2008**, *319*, 247–251.
10. Regen, S. L.; Quici, S.; Liaw, S. J. *J. Org. Chem.* **1979**, *44*, 2029–2030.
11. Regen, S. L.; Quici, S.; Ryan, M. D. *J. Am. Chem. Soc.* **1979**, *101*, 7629–7630.
12. (a) Balaban, A. T.; Dinculescu, A.; Dorofeenko, G. N.; Fischer, G. W.; Koblik, A. V.; Mezheritskii, V. V.; Schroth, W. *Advances in Heterocyclic Chemistry*; A. R. Katritzky (Ed.); Academic: New York, 1982, vol. 2, suppl 1; (b) Balaban, A. T.; Schroth, W.; Fischer, G. W. Pyrylium salts. In *Advances in Heterocyclic Chemistry*; A. R. Katritzky (Ed.); Academic: New York, 1969, vol. 10, p. 241, and references therein.