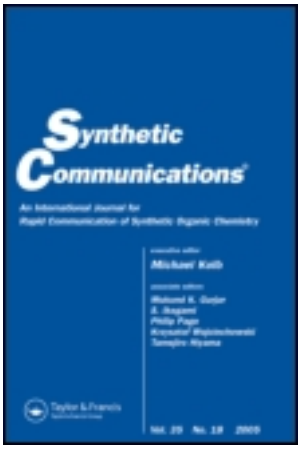

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Efficient Synthesis of Bifenazate

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Abstract: The synthesis of bifenazate using a two-step procedure has been accomplished with an overall yield of 26%. The procedure involved the Lewis acid–catalyzed electrophilic aromatic substitution of 4-methoxybiphenyl with diisopropyl azodicarcoxylate (DIAD) to give a hydrazinedicarboxylate intermediate that was then subjected to a decarboxylation reaction to give bifenazate.

Keywords: Bifenazate, diisopropyl azodicarboxylate, fluoroalcohols, 4-methoxybiphenyl, nitromethane

INTRODUCTION

Bifenazate[1,2] (**1**) is an acaricide effective against pest mites such as European red mites and two-spotted spider mites, but has low toxicity to predaceous mites and other beneficial arthropods (Scheme 1). In addition to being safe to nontargets, bifenazate also has very little impact on the environment and is highly compatible with the integrated pest-management programs. The combining advantages have earned bifenazate the designation of a "reduced risk" pesticide from the U.S. Environmental Protection Agency.

Three different methods, as depicted in Scheme 2, have been reported for the preparation of bifenazate.[3–5] There are advantages and disadvantages of each of the reported methods, but all these methods require a total of three steps in the preparation of bifenazate from commercially available starting materials. It remains important to search for alternative and more efficient

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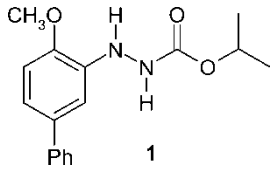
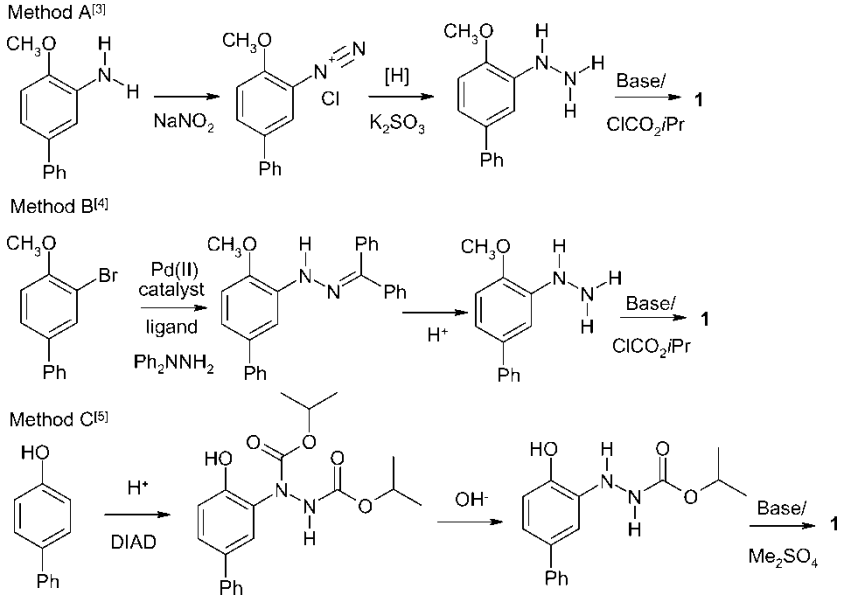


Scheme 1.

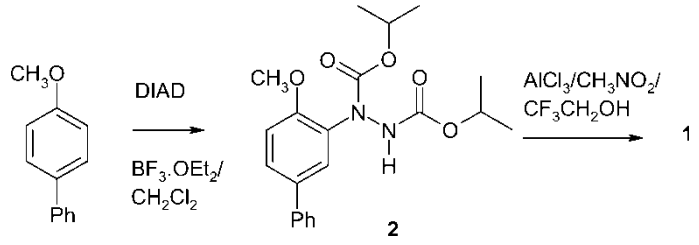
methods to reduce the cost and time for the production of this commercial acaricide. During our search for an alternative route, we have developed a two-step procedure for the preparation of bifenazate from relatively inexpensive and commercially available 4-methoxybiphenyl (Scheme 3). Our method offers the shortest alternative route to bifenazate in two easy-to-handle reaction steps.

RESULTS AND DISCUSSION

The electrophilic aromatic substitution of electron-rich arenes such as phenolic derivatives with electron-deficient azodicarboxylic acid esters under thermal or acid catalysis is an efficient method for the introduction of a masked hydrazine or amino group to an arene.[5,6] Although the introduction



Scheme 2.



Scheme 3.

of a hydrazine functionality on 4-methoxybiphenyl via this approach has not been reported, we have been successful in adapting this approach to afford the bifenazate intermediate **2** in 57% yield after purification by chromatography. The optimum condition for this reaction involved the use of $BF_3 \cdot OEt_2$ as catalyst and dichloromethane as solvent. The yields of this reaction dropped significantly when the reaction was performed under heterogeneous conditions using catalysts of lower solubility or reactivity. For instances, the use of $AlCl_3$, ZnI_2, $ZnCl_2$, $ZrCl_4$, and H_2SO_4 as catalyst failed to afford any significant amount of **2**, giving predominantly the unreacted 4-methoxybiphenyl and a mixture of unidentified impurities. Solvents such as ether, toluene, and ethyl acetate were also found to be unsuitable for the reaction, affording hydrazinedicarboxylate **2** in lower and inconsistent yields.

Our initial attempts to selectively cleave N1-carboxylate group using acid and base hydrolysis to afford bifenazate were totally unsuccessful. The hydrolysis reactions were performed using aqueous HCl, H_2SO_4, and NaOH in solvents such as 2-propanol, toluene, and DMSO under various conditions. In all instances, we either obtained the unreacted hydrazinedicarboxylate **2** or observed the decarboxylation reaction occurring at an extent where predominantly 4-methoxybiphenyl was isolated as decomposition product. Other decarboxylation attempts that we made without success were the nonsaponification S_N2-type dealkylation reactions using aluminum chloride as catalyst and a thiol or sodium iodide as nucleophile.

During our search for a method to prepare bifenazate from hydrazinedicarboxylate **2**, we have discovered a facile method for selective deprotection of isopropyl esters, carbamates, and carbonates with aluminum chloride in nitromethane.[7] When the same procedure was applied to hydrazinedicarboxylate **2**, a minor amount of bifenazate was observed when the reaction was largely incomplete after overnight stirring at room temperature. This encouraging observation prompted us to investigate other conditions to increase the rate of the deprotection reaction without compromising the selectivity. Increasing the reaction temperature somewhat facilitated the reaction but significantly increased the amount of impurities formed. We investigated the use of other acids, such as $TiCl_4$, BF_3OEt_2, $SnCl_4$, $ZnCl_2$, $ZrCl_4$, trifluoroacetic acid, H_2SO_4, Et_3Al, $(Et_2AlCl)_2$, and trifluorosulfuric acid, even though we

have previously observed that $AlCl_3$ was the acid of choice for activating the deprotection reaction. $TiCl_4$ afforded a result similar to that obtained for $AlCl_3$, whereas the remaining acids were found to be ineffective as activators, giving either no reactions or a mixture of unknown components. When elevated temperatures were employed, most of these ineffective acids had only facilitated the formation of impurities. The unsuccessful attempts caused us to turn our attention to other solvents such as ethyl acetate, nitrobenzene, dichloromethane, and ether. These attempts were similarly unsuccessful. Because the use of a fluorous phase has been proven to present some advantages in certain organic reactions,[8] we chose to use a fluoroalcohol as cosolvent. Using a 1 : 1 mixture of nitromethane and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent and $AlCl_3$ as catalyst, the decarboxylation reaction was found to be more than 80% complete by TLC analysis after stirring overnight at 40°C. Bifenazate appeared to be the major product, and 4-methoxybiphenyl and an unknown component, presumably the N2-decarboxlated product, were present as minor components. The reaction was subsequently quenched with water and worked up to afford bifenazate in 46% yield after purification by column chromatography. 2,2,2-Trifluoroethanol was found to be as equally suitable a cosolvent as HFIP. Using nitromethane or the fluoroalcohols alone gave lower yields, and other ratios did not improve upon the yield obtained using the 1 : 1 mixture.

In conclusion, we have successfully synthesized bifenazate from 4-methoxybiphenyl in an overall yield of 26% using a two-step procedure. Although it was extremely challenging to develop the procedure, each reaction step was easy to handle and did not require the use of special apparatus or an inert atmosphere.

EXPERIMENTAL

Melting points were measured on a hot-stage instrument and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 FT instrument using tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 283B spectromer. HRMS/mass spectra were obtained on an Analytical VG 7070E-HP instrument. Aldrich 28859-4 silica gel was used for all column chromatography.

Hydrazinedicarboxylate 2

$BF_3 \cdot OEt_2$ (0.7 mL) was added to a solution of 4-methoxybiphenyl (1.0 g, 5.4 mmol) in dichloromethane (6 mL) at room temperature. The solution mixture was cooled to 0°C, and DIAD (2.1 mL, 5.4 mmol) was added dropwise over a period of 10 min. The resulting blue-green solution was stirred at that temperature for 1 day and allowed to warm to room temperature

before it was worked up by adding water (10 mL) and extracting with dichloromethane (2 × 10 mL). The extract was concentrated under reduced pressure, and the crude product was chromatographed on silica gel (30–50% ethyl acetate/hexanes) to give hydrazinedicarboxylate **2** as a beige solid (1.2 g, 57%): mp 137–137.5°C; IR (KBr): 3600 (NH), 1735 (CO), 1690 (CO) cm^{-1}; ^1H NMR (DMSO-d6) δ: 1.19 (br d, 12H, $J = 6.0$); 3.82 (s, 3H), 4.82 (br septet, 2H, $J = 3.0$), 7.15 (m, 1H), 7.33 (m, 1H), 7.45 (m, 2H), 7.53–7.62 (m, 4H), 9.83 (br s, NH); ^{13}C NMR ($CDCl_3$) δ: 22.37 (2 × CH_3), 22.45 (2 × CH_3), 56.11 (CH), 70.09 (CH), 70.94 (CH_3), 111.95 (2 × C), 127.15 (2 × CH), 127.33 (CH), 127.93 (2 × CH), 129.12 (3 × CH), 134.13 (C), 140.37 (C), 154.38 (C), 156.15 (C); mass spectrum m/e (% rel): 386 (9%, M^+), 300 (34%, M-CO_2iPr), 301 (MH-CO_2iPr, 50%); HRMS calcd. for $[C_{21}H_{26}N_2O_5\ H]^+$ 387.1920, found $[MH]^+$ 387.1927.

Bifenazate[1]

2,2,2-Trifluoroethanol (2 mL) was added to a stirred suspension of hydrazinedicarboxylate **2** (0.52 g, 1.34 mmol) in nitromethane (2 mL) at room temperature. The resulting green mixture was cooled to 0°C, $AlCl_3$ (0.44 g, 3.30 mmol) was added, and the mixture was subsequently heated at 40°C with stirring for 12 h. The resulting red solution was cooled to 0°C, water was added (15 mL) slowly, and it was then stirred at room temperature for 10 min. The mixture was extracted with ethyl acetate (3 × 5 mL), and the combined organic phase was concentrated under reduced pressure. The resulting brown residue was chromatographed on silica gel (30–50% ethyl acetate/hexanes) to afford bifenazate as beige solid (0.19 g, 46%). Melting points[9] and ^1H NMR spectral data[3a] were consistent with those published previously.

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REFERENCES

1. Dekeyser, M. A.; McDonald, P. T.; Angle, G. W., Jr. The discovery of bifenazate, a novel carbazate acaricide. *Chimia* **2003**, *57* (11), 702–704.
2. Dekeyser, M. A. Uniroyal Chemical develops a new miticide. *Can. Chem. News* **2000**, *52* (7), 11–12.
3. (a) Dekeyser, M. A.; McDonald, P. T. Insecticidal phenylhydrazine derivatives. US Patent 5,367,093, November 22, 1994; (b) Jin, H. Process for the preparation

of insecticidal phenylhydrazine derivatives. US Patent 6,278,022, August 21, 2001.
4. Park, S.B.; Chee, G.-L.; Dekeyser, M. A. 4-Methoxybiphenyl hydrazone derivatives.. US Patent 6,706,895, March 16, **2004**.
5. Chee, G. L.; Park, S. B.; Dekeyser, M. A. 4-Hydroxybiphenyl hydrazide derivatives. US Patent 6,093,843, July 25, 2000.
6. (a) Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. Synthesis of aromatic amines from electron-rich arenas and bis(2,2,2-trichloroethyl) azodicarboxylate. *Tetrahedron Lett.* **1993**, *34* (15), 2441–2444; (b) Mitchell, H.; Leblanc, Y. Amination of arenes with electron-deficient azodicarboxylates. *J. Org. Chem.* **1994**, *59*, 682–687; (c) Leblanc, Y.; Boudreault, N. Para-directed amination of electron-rich arenas with bis(2,2,2-trichloroethyl) azodicarboxylate. *J. Org. Chem.* **1995**, *60*, 4268–4271; (d) Yadav, J. S.; Subba Reddy, B. V.; Mahesh Kumar, G.; Madan, C. $InCl_3$-SiO_2 catalyzed electrophilic amination of arenas: A facile and rapid synthesis of aryl hydrazides. *Synlett* **2001**, *11*, 1781–1783; (e) Bombek, S.; Lanarsic, R.; Kocevar, M.; Saint-Jalmes, L.; Desmurs, J-R.; Polanc, S. $ZrCl_4$-promoted halogen migration during an electrophilic amination of halogenated phenols. *Chem. Commun.* **2002**, 1494–1495.
7. Chee, G. Selective deprotection of isopropyl esters, carbamates and carbonates with aluminum chloride. *Synlett* **2001**, *10*, 1593–1595.
8. Ravikumar, K. S.; Zhang, Y. M.; Begue, J-P.; Bonnet-Delphon, D. Role of hexafluoro-2-propanol in selective oxidation of sulfide to sulfoxide: Efficient preparation of glycosyl sulfoxides. *Eur. J. Org. Chem.* **1998** (2937–2940), and references cited therein.
9. Thompkins, G. J. US EPA new pesticide fact sheet: Bifenazate. EPA-738-F-97, June 1999.