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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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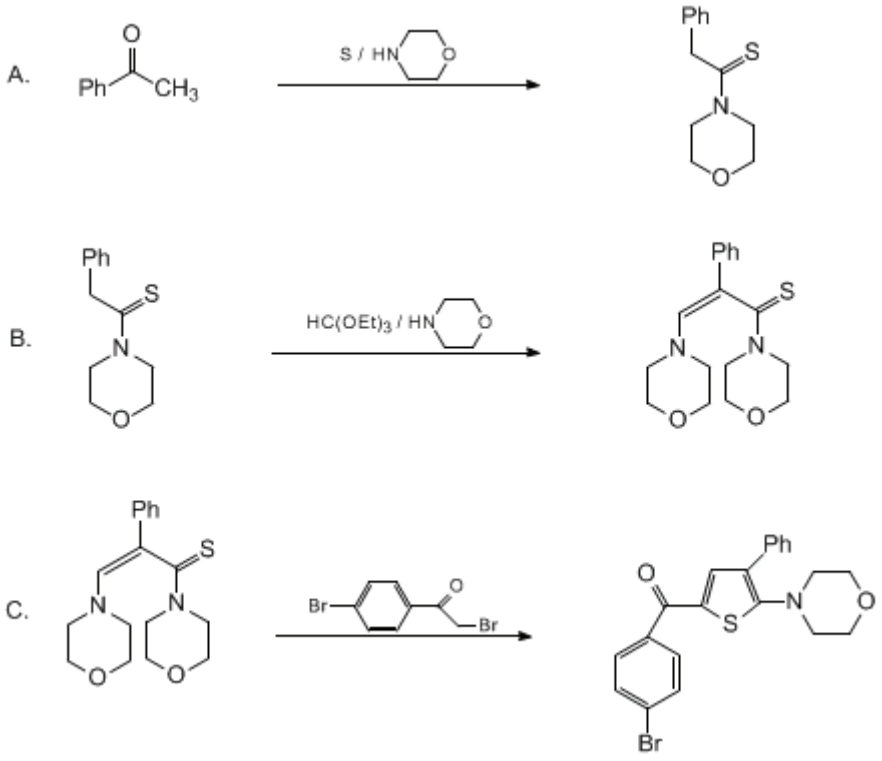
3-MORPHOLINO-2-PHENYLTHIOACRYLIC ACID MORPHOLIDE AND 5-(4-BROMOBENZOYL-2-(4-MORPHOLINO)-3-PHENYLTHIOPHENE

[(Morpholine, 4-[3-(4-morpholinyl)-2-phenyl-1-thioxo-2-propenyl]-,) and (Thiophene, 5-(4-bromobenzoyl)-2-(4-morpholino)-3-phenyl-)]



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1. Procedure

Caution! Part A should be carried out in an efficient hood to avoid exposure to noxious vapors (hydrogen sulfide).

A. *Phenylthioacetic acid morpholide*. A 100-mL, round-bottomed flask is charged with 24.0 g (0.2 mol) of acetophenone, 1 g of p-toluenesulfonic acid monohydrate, 36.0 g (0.41 mol) of morpholine, and 6.4 g (0.2 mol) of sulfur (Note 1). The flask is equipped with a reflux condenser and is heated at reflux for 3 hr (Note 2). The resulting reddish-brown solution is poured into 100 mL of stirred hot methanol (55–60°C). The wall of the beaker is scratched with a glass rod for seeding. The beaker is sealed with aluminum foil and put into a refrigerator for 6 hr (Note 3). The resulting crystalline product is filtered and washed twice with ice-cold methanol (10 mL). The material (22.2 g, mp 69–79°C, almost colorless) is recrystallized by adding 25 mL of methanol and 25 mL of water and heating at reflux, followed by slow addition of methanol (about 58 mL) until complete solution is obtained. After the sides of the flask are scratched, the solution is cooled in a refrigerator for about 10 hr; 21.9 g (49.5%) (Note 4) of the pure product is obtained, mp 77.5–79°C.

B. *3-Morpholino-2-phenylthioacrylic acid morpholide*. A distillation apparatus (250-mL, round-

bottomed flask, distillation head, thermometer, condenser and receiver) equipped with a magnetic stirrer is charged with 22.3 g (0.1 mol) of phenylthioacetic acid morpholide, 26.1 g (0.3 mol) of morpholine and 67 mL (0.4 mol) of triethyl orthoformate (Note 5). The flask is heated in a heating bath (bath temperature ~ 160°C) for 8 hr. During this time, ethanol is distilled continuously from the reaction (about 18 mL). Further raising the temperature of the bath to 180°C gives rise to the distillation of excess morpholine and triethyl orthoformate (38 mL, bp 128–130°C) from the orange solution within 30 min (Note 6). The mixture is evaporated under reduced pressure (rotary evaporator, bath temperature ~ 80°C). The remaining crystalline material is dissolved in 30 mL of chloroform and 150 mL of hot methanol (about 60°C). The solution is allowed to cool to room temperature (Note 7) and is put into a freezer (−24°C) for 12 hr. The light yellow product is filtered and washed with methanol (30 mL) followed by diethyl ether (30 mL). After drying in the open air for 18 hr, 29.4 g (92%) (Note 8) of pure material is obtained, mp 156–156.5°C (Note 9).

C. *5-(4-Bromobenzoyl)-2-morpholino-3-phenylthiophene*. A mixture of 3.18 g (0.01 mol) of 3-morpholino-2-phenylthioacrylic acid morpholide, 2.8 g (0.01 mol) of 4-bromophenacyl bromide, and 50 mL of methanol is heated to boiling. After the addition of a solution of 1.01 g (0.01 mol) of triethylamine in 10 mL of methanol to the mixture, the reaction is allowed to heat at reflux for 10 min. The reaction mixture is then cooled to 0°C in a refrigerator for 1 hr. The yellow crystalline product is collected by filtration and washed with 20 mL of cold methanol. After drying in the open air for 18 hr, 4.15 g (97%) of analytically pure product is obtained, mp 176–177°C (mp[2] 175°C) (Note 10). Although not necessary, the material can be recrystallized from acetonitrile.

2. Notes

1. All chemicals were obtained from the Aldrich Chemical Company, Inc. It is advisable to distill acetophenone and morpholine. The sulfur should be small particles and must not form lumps. Excess morpholine is generally recommended in Willgerodt-Kindler reactions.
2. The reflux condenser should be connected by a gas outlet and tubing directly to the hood pipe to prevent hydrogen sulfide from entering the laboratory atmosphere.
3. If crystallization fails, a small amount of the solution is evaporated, cooled in an ice/sodium chloride bath, and scratched with a glass rod. The resulting crystals are used to seed the main solution.
4. a) The reported yield[3] of 94% could not be achieved. The amount of sulfur can be increased to 12.4 g (0.2 mol) giving a higher yield of phenylthioacetic acid morpholide that contains some unreacted sulfur and a yellow impurity (2-morpholin-4-yl-1-phenyl-2-thioxoethanone) that is difficult to remove. b) Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.37 (m, 2 H), 3.61 (m, 2 H), 3.72 (m, 2 H), 4.34 (s, 2 H), 4.34 (m, 2 H), 7.23 (m, 1 H), 7.31 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 50.06, 50.50, 50.70, 65.99, 66.21, 127.01, 127.01, 127.66, 128.84, 135.70, 199.91.
5. Triethyl orthoformate was distilled. Trimethyl orthoformate can not be used since no reaction occurs. Excess morpholine and triethyl orthoformate are used as solvents to achieve smooth solution. The amounts of both of these reagents can be increased without affecting the yield.
6. TLC of the remaining solution (0.25-mm Whatman precoated silica gel plate, 33% ethyl acetate in hexanes) does not show any starting phenylthioacetic acid morpholide.
7. Crystallization of the pure product begins after slight cooling.
8. Additional product can be obtained by evaporating the combined mother liquor, adding 25 mL of methanol to the remaining oil, and cooling the resulting solution to −24°C.
9. The product consists of a mixture of E/Z isomers[4] in an approximate ratio of 15:85; R_f = 0.35 and 0.25 (0.25-mm Whatman precoated silica gel plate, 33% ethyl acetate in hexanes). Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80; S, 10.07, Found: C, 64.38; H, 6.99; N, 8.80; S, 10.18. IR (KBr) cm^{-1}: 1611, 1586, 1440, 1429, 1413, 1236, 1226, 1116; Z-isomer (major isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 124.8, 128.5 (C2',C3'-C_6H_5), 125.3 (C4'-C_6H_5), 139.3 (C1'-C_6H_5), 112.6 (C2), 137.5 (C3), 198.9 (C1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.07 (s, HC=C); E-isomer (minor isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 126.4 (C4'-C_6H_5), 128.1, 129.9 (C2',C3'-C_6H_5), 138.3 (C1'-C_6H_5), 115.2 (C2), 147.4 (C3), 203.3 (C1).
10. The spectral data for the title compound are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.05 (m, 4 H), 3.71 (m, 4 H), 7.21 (dddd, 1 H), 7.35 (m, 2 H), 7.46 (s, 1 H), 7.50–7.53 (m, 2 H), 7.57 (ddd, 2 H), 7.65 (ddd, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.79, 66.11, 126.21, 126.28, 127.29, 127.67, 128.13, 130.08, 130.31, 131.57, 135.51, 137.12, 138.64, 162.80, 185.84.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

3-Aminothioacrylic acid amides are versatile β-dicarbonyl derivatives that have found widespread use as C-C-C and C-C-C-S building blocks in the synthesis of heterocyclic and open chain products.[5,6] To date, 2-arylthioacrylmorpholides with mainly a 3-dimethylamino leaving group have been prepared by the Vilsmeier-Haack reaction of arylthioacetic acid amides with DMF/$POCl_3$.[7,8] This synthesis is not convenient since the resulting 3-dimethylaminothioacrylic acid morpholides must be isolated as hydroperchlorates, the yields are occasionally low, and in a number of cases (especially if other amino groups beside the morpholino or dimethylamino are found in the products, or if the aryl group is ortho-substituted) no stable crystalline material is obtained. With the present procedure,[9] a very reliable synthesis of 3-morpholinothioacrylic acid amides with a wide variety of 2-aryl substituents has been elaborated. Instead of triethyl orthoformate/morpholine, the non-commercially available trismorpholinomethane[10] can be used,[9] also enabling the synthesis of the 2-unsubstituted 3-morpholinothioacrylic acid morpholide. In addition to the well known Willgerodt-Kindler reaction,[11] the starting thioacetamides can also be obtained by other methods such as reaction of styrenes with sulfur and amines,[12] and the reaction of arylthioacetic acid thiol ester with amines.[13] Furthermore the thioamide amino group of the synthesized 3-morpholinothioacrylic acid amides can also be monosubstituted. Through the use of pyrrolidine, 3-pyrrolidinothioacrylic acid amides can be obtained. Generally the procedure is very simple and safe. Scale-up can be effected without incident and very pure products are obtained. Since the 3-morpholino substituent usually acts as a leaving group in further synthetic applications, the same reactivity is found as in the well investigated 2-aryl-3-dimethylaminothioacrylic acid morpholides.

The mechanism of the formation of 3-aminothioacrylic amides from arylthioacetic acid amides and ortho ester amine is likely to resemble similar aminomethinylation reactions of other CH-acidic substrates.[14]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

hexanes

$POCl_3$

3-Morpholino-2-phenylthioacrylic acid morpholide

3-MORPHOLINO-2-PHENYLTHIOACRYLIC ACID MORPHOLIDE AND 5-(4-BROMOBENZOYL-2-(4-MORPHOLINO)-3-PHENYLTHIOPHENE

(Morpholine, 4-[3-(4-morpholinyl)-2-phenyl-1-thioxo-2-propenyl]-

Thiophene, 5-(4-bromobenzoyl)-2-(4-morpholino)-3-phenyl-)

ethanol (64-17-5)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

hydrogen sulfide (7783-06-4)

sulfur (7704-34-9)

Acetophenone (98-86-2)

triethyl orthoformate (122-51-0)

DMF (68-12-2)

pyrrolidine (123-75-1)

morpholine (110-91-8)

triethylamine (121-44-8)

trimethyl orthoformate (149-73-5)

5-(4-Bromobenzoyl)-2-morpholino-3-phenylthiophene (86673-62-3)

Phenylthioacetic acid morpholide (949-01-9)

4-bromophenacyl bromide (99-73-0)

2-morpholin-4-yl-1-phenyl-2-thioxoethanone

trismorpholinomethane

p-toluenesulfonic acid monohydrate (6192-52-5)