Base-Promoted in Situ Generation of Methyl Acrylate from Dimethyl 3,3′-Dithiodipropionate. Application to N-Alkylation of Heterocycles

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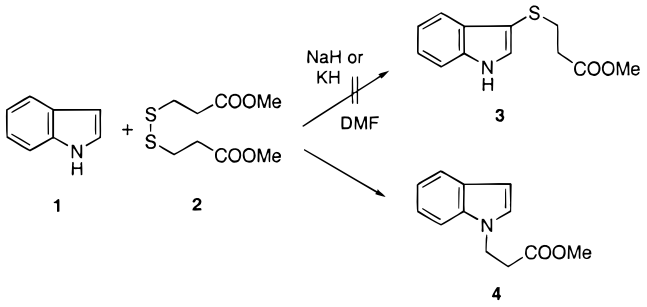
In basic medium, dimethyl 3,3′-dithiopropionate generates methyl acrylate, which serves in situ as a source of propionate moiety. This property was applied to the alkylation of indoles and other nitrogen heterocycles leading to a series of 3-(heteroaryl-substituted) propionates. A mechanistic rationale for the generation of acrylate is presented along with supportive experimental data.

Several years ago, we reported[1] on a novel method for the synthesis of 3-arylthio indoles by reaction of the sodium anion of indole (**1**) with diaryl disulfides in DMF solution. We also reported that the process was inefficient when applied to dialkyl disulfides, such as dimethyl disulfide, which did not lead to the corresponding 3-alkylthio indoles. Only unreacted indole or decomposition products were obtained in these cases. However, we have since encountered a very interesting result when dimethyl 3,3′-dithiodipropionate (**2**) was used as the substrate. In this case, the reaction led cleanly, in 66% yield, to a compound that was an N-substituted derivative, with no trace of the expected methyl 3-(3-indolylthio)propionate (**3**).[2] The structure was identified as methyl 3-(1-indolyl)propionate (**4**, Scheme 1) on the basis of its ^{1}H NMR spectrum, which showed the presence of all of the ring protons of the indole as well as a propionate moiety, while mass spectral and elemental analyses revealed the absence of sulfur in the molecule. Compound **4** has been previously prepared from the reaction of indole anion with methyl acrylate[3,4] (72% and 54% yields) or methyl 3-bromopropionate[4] (78%) or alternatively by a palladium-catalyzed carbonylation reaction of indole using CO and ethylene in methanol (40%).[5] The unexpected formation of **4** under our conditions led us to study the scope of the reaction and especially to obtain insight on its mechanistic rationalization.

In a study of the scope and conditions of this novel reaction, we found that the process is generally applicable to indole derivatives and also to other nitrogen heterocyles, such as carbazole, norharman (i.e., pyrido[3,4-*b*]-indole), indazole, and benzimidazole. An examination of various bases led to the conclusion that KH affords slightly superior results than NaH, while other bases such as LDA, cesium carbonate, or NaHMDS are generally less efficient. Table 1 lists the results obtained with KH as base (1.2 equiv), with 1.05 equiv of **2** in DMF at room temperature. Variations on the proportions of base

Scheme 1



or disulfide lead to lower yields and more side products. In all of the cases studied, various amounts of the unreacted starting heterocycle remained. In the case of indole, the yields obtained were comparable to those reported when acrylate or 3-bromopropionate were used. We could not find literature results with the other indole derivatives of Table 1 or the other heterocycles.

The fact that N-substituted products were obtained led us to initially suspect that the reaction might proceed by initial N-sulfenylation, leading, in the case of indole, to a putative 1-indolylsulfenamide, which via a sulfur extrusion process would afford compound **4**. This explanation was rapidly abandoned when the reaction was applied under the same conditions to dimethyl dithiodiglycolate and dimethyl 4,4′-dithiodibutanoate. No trace of the *N*-acetate or *N*-butanoate analogues of **4**, the expected products if the N-sulfenylation hypothesis were correct, were produced. In addition, although reports of isolated N-sulfenylated indoles have appeared in the literature,[6] these compounds were subsequently shown to be 3-sulfenylated analogues.[7]

It seemed to us that a more plausible mechanistic explanation for the formation of **4** and analogues from reactions involving 3,3′-dithiodipropionate would be to consider the possibility of generation of methyl acrylate under the basic reaction conditions, the latter acting as the source of the propionate unit. We proceeded to run a control experiment, where we recorded the ^{1}H NMR spectrum of a solution of **2** in deuterated DMF to which

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(2) Hamel, P.; Girard, Y.; Atkinson, J. G. *J. Org. Chem.* **1992**, *57*, 2694.
(3) Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285.
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(5) Hegedus, L. S.; Winton, P. M.; Sudarsanan, V. *J. Org. Chem.* **1981**, *46*, 2215.
(6) (a) Tulecki, J.; Szulc, C. *Ann. Pharm. (Poznan)* **1969**, *7*, 3. (b) Tulecki, J.; Szulc, C. *Ibid.* **1973**, *10*, 3.
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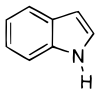
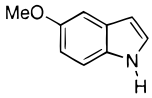
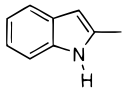
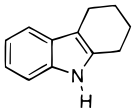
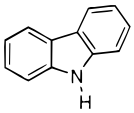
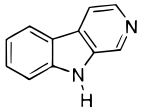
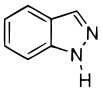
Table 1. Reaction of Various Heterocycles with Potassium Hydride (1.2 Equiv) and 2 (1.05 Equiv) in DMF

Substrate	Reaction Time (h)	Yield[a] (%)	Product
	1	66	**4**
	1.5	58	**6**
	1.5	50 (57)	**7**
	3	40 (45)	**8**
	18	63 (70)	**9**
	18	61 (72)	**10**
	1.5	50 (74)	**11**
	18	41 (49)	**12**

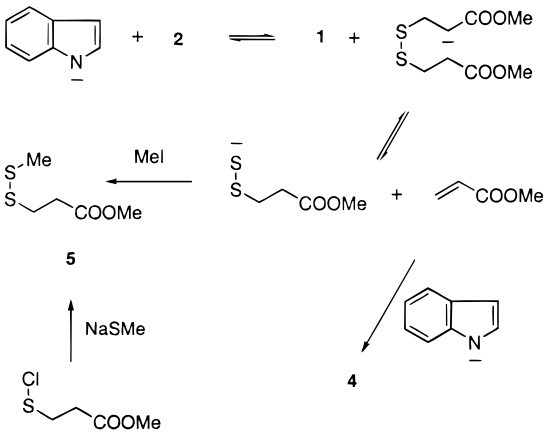
[a] Isolated yield; value in parentheses is yield based on recovered starting material.

some NaH had been added. Typical signals in the 6.1−6.6 ppm region of the spectrum indicated that indeed acrylate had been generated, presumably via abstraction of a proton α to one of the ester groups followed by elimination of a sulfur-containing counterpart bearing a negative charge, all in equilibrium with **2**. Under the actual conditions of the alkylation reactions, the anion of the heterocycle presumably causes the abstraction of the proton of the dithiodipropionate.

The identity of the resulting sulfur-containing counterpart to the acrylate remained to be established. To this end, a solution of **2** in DMF was again treated with NaH, leading to the usual dark green solution always observed in these reactions. Methyl iodide was then added in an attempt to trap the side product in a form that could be identified. From this mixture we isolated in 44% yield an adduct that we identified as the mixed disulfide **5** (Scheme 2). The structure was established via ^{1}H NMR and elemental analysis and also by direct synthesis from 2-carbomethoxyethylsulfenyl chloride and sodium thiomethoxide.

We know nothing about the longevity of the sulfur-containing counterpart in the absence of trapping agent,

Scheme 2



as we have not isolated the other components of the crude reaction mixtures, but we do not believe that a second equivalent of acrylate is generated from it.

Thus, it appears that in the reaction medium leading to the alkylation, a series of equilibria exist, as illustrated in Scheme 2 for indole, between the indole anion, **2**, indole itself, and the anion of **2**, the latter in equilibrium with methyl acrylate and the negatively charged eliminated disulfide counterpart. The irreversible addition of the indole anion onto acrylate drives the process toward the N-alkylated end-product.

We could not find any report in the literature on the generation of acrylate from 3′,3′-dithiodipropionate. The only analogy we found was a study[8] on the decomposition of 3,3′-dithiodipropionic acid and its diethyl ester in aqueous sodium hydroxide solution, leading to mixtures of 2-mercaptopropionic acid and 2-mercapto-3-hydroxypropionic acid, with no mention of acrylic acid or acrylate being produced.

In conclusion, in situ generation of methyl acrylate from dimethyl 3,3′-dithiodipropionate represents a novel approach for the introduction of a propionate moeity onto nitrogen heterocycles. The reagent is easily obtained by esterification of the inexpensive 3,3′-dithiodipropionic acid. It is stable and can be distilled and stored at room temperature for prolonged periods of time. In contrast, acrylates are highly irritating lachrymators and polymerize on storing in the absence of stabilizing agents. Bromopropionates are also irritants and lachrymators, and as for all reactive alkyl halides require precautions in handling. The use of dithiodipropionate presents an alternative to the handling of these offensive substances, while affording comparative yields. We are in the process of examining the application of our methodology to C-alkylation.

Experimental Section

Commercial reagents were used without further purification or drying. The use of a nitrogen atmosphere was required. ^{1}H NMR and ^{13}C NMR spectra were recorded in acetone-d_6 solution on a 400 MHz instrument and chemical shifts are reported in ppm. Elemental analyses were provided by Guelph Chemical Laboratories Ltd. Guelph, Ontario, and by Oneida Research Services, Inc. Whitesboro, NY. High-resolution mass spectra (HRMS-FAB$^+$) were obtained at the Biomedical Mass Spectrometry Unit, McGill University, Montreal, Québec,

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Canada. Progress of the reactions was monitored by TLC silica gel plates and purifications were performed using flash silica gel columns.

General Procedure for N-Alkylation. **Methyl 3-(1-Indolyl)propionate (4).** To a suspension of 180 mg of KH 35 wt % dispersion in mineral oil (1.57 mmol) in 5 mL of dry DMF was added 153 mg of indole (**1**) (1.3 mmol) in portions, and the reaction was stirred at room temperature until evolution of hydrogen had ceased (approximately 30 min). A solution of 327 mg of dimethyl 3,3′-dithiodipropionate (**2**) (1.37 mmol) in 1 mL of dry DMF was then added, and the resulting green mixture was stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous ammonium chloride solution, and the aqueous layer was extracted three times with ether. The combined extracts were washed twice with water and then with brine, dried ($MgSO_4$), and evaporated to a residue that was chromatographed eluting with a 5:95 mixture of toluene and hexane to afford 175 mg of **4** (66%) as a thick oil: ^{1}H NMR δ 2.85 (t, 2H), 3.60 (s, 3H), 4.50 (t, 2H), 6.42 (d, 1H), 7.02 (t, 1H), 7.15 (t, 1H), 7.27 (d, 1H), 7.45 (d, 1H), 7.54 (d, 1H); ^{13}C NMR δ 35.2, 42.3, 51.8, 101.9, 110.2, 119.9, 121.5, 122.1, 128.9, 129.6, 136.7, 172.1. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.64; H, 6.56; N, 6.82.

This method was followed to prepare the following compounds at the temperature and for the time indicated in Table 1. In some cases, ethyl acetate was used for extraction due to low solubility of the products in ether.

Methyl 3-(1-(5-methoxyindolyl))propionate (6): thick oil; ^{1}H NMR δ 2.83 (t, 2H), 3.59 (s, 3H), 3.78 (s, 3H), 4.45 (t, 2H), 6.33 (d, 1H), 6.80 (d, 1H), 7.04 (s, 1H), 7.22 (s, 1H), 7.34 (d, 1H); ^{13}C NMR δ 35.3, 42.5, 51.8, 55.7, 101.5, 103.1, 110.9, 112.3, 129.4, 130.1, 131.9, 155.0 172.2. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.58; H, 6.24; N, 5.85.

Methyl 3-(1-(2-methylindolyl))propionate (7): thick oil; ^{1}H NMR δ 2.45 (s, 3H), 2.77 (t, 2H), 3.59 (s, 3H), 4.44 (t, 2H), 6.18 (s, 1H), 6.96 (t, 1H), 7.06 (t, 1H), 7.36 (d, 1H), 7.41 (d, 1H); ^{13}C NMR δ 12.5, 34.8, 39.3, 51.8, 100.9, 109.8, 119.9, 120.2, 121.1, 129.3, 137.2, 137.3, 172.1. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.04; H, 6.80; N, 6.37.

Methyl 3-[9-(1,2,3,4-tetrahydrocarbazolyl)]propionate (8): thick oil; ^{1}H NMR: δ 1.79−1.85 (m, 2H), 1.88−1.94 (m, 2H), 2.63−2.67 (m, 2H), 2.72−2.83 (m, 4H), 3.59 (s, 3H), 4.37 (t, 2H), 6.97 (t, 1H), 7.06 (t, 1H), 7.36 (t, 2H); ^{13}C NMR: δ 21.7, 22.4, 23.9, 24.0, 35.0, 39.1, 51.8, 109.6, 109.9, 118.3, 119.3, 121.2, 128.6, 135.9, 136.8, 172.1. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.30; H, 7.54; N, 5.37.

Methyl 3-(9-carbazolyl)propionate (9): white solid; mp 65−66 °C; ^{1}H NMR δ 2.89 (t, 2H), 3.55 (s, 3H), 4.73 (t, 2H), 7.21 (t, 2H), 7.46 (t, 2H), 7.60 (d, 2H), 8.12 (d, 2H); ^{13}C NMR δ 33.8, 39.4, 51.8, 109.9, 119.8, 120.9, 123.7, 126.5, 140.9, 172.2. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.67; H, 6.00; N, 5.50.

Methyl 3-(9-(pyrido[3,4-*b*]indolyl))propionate (10): thick oil; ^{1}H NMR δ 2.95 (t, 2H), 3.52 (s, 3H), 4.79 (t, 2H), 7.27 (t, 1H), 7.59 (t, 1H), 7.67 (d, 1H), 8.01 (d, 1H), 8.19 (d, 1H), 8.41 (d, 1H), 9.07 (s, 1H); ^{13}C NMR δ 33.9, 39.7, 51.8, 110.8, 115.0, 120.5, 122.0, 122.5, 128.8, 129.0, 133.6, 137.0, 139.8, 141.6, 172.2; HRMS calcd for $C_{15}H_{15}N_2O_2$ (M + H) 255.11332, found 255.11341.

Methyl 3-(1-indazolyl)propionate (11): thick oil; ^{1}H NMR δ 2.97 (t, 2H), 3.57 (s, 3H), 4.67 (t, 2H), 7.12 (t, 1H), 7.38 (t, 1H), 7.63 (d, 1H), 7.73 (d, 1H), 8.00 (s, 1H); ^{13}C NMR δ 34.6, 44.7, 51.8, 110.2, 121.2, 121.5, 124.9, 126.7, 133.8, 140.4, 172.0. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.22; H, 6.10; N, 13.34.

Methyl 3-(1-benzimidazolyl)propionate (12): thick oil; ^{1}H NMR δ 2.95 (t, 2H), 3.59 (s, 3H), 4.58 (t, 2H), 7.21−7.26 (m, 2H), 7.58 (d, 1H), 7.67 (d, 1H), 8.09 (s, 1H); ^{13}C NMR δ 34.7, 40.9, 51.9, 110.7, 120.6, 122.3, 123.2, 134.6, 144.6, 145.0, 171.9; HRMS calcd for $C_{11}H_{13}N_2O_2$ (M + H) 205.0977, found 205.09767.

3-Methyldisulfanylpropionic Acid Methyl Ester (5). Method A. Iodomethane (1.5 mL, 24 mmol) was added to a suspension of 371 mg of NaH 60% w/w dispersion in mineral oil (9.28 mmol) in 20 mL of dry DMF cooled to 0 °C. A solution of 1.80 g of **2** (7.57 mmol) in 10 mL of dry DMF was then added, and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with saturated aqueous ammonium chloride solution and extracted three times with ether. The combined extracts were washed twice with water and then with brine, dried ($MgSO_4$), and evaporated to a residue that was chromatographed on silica gel with a 1:9 mixture of ether and hexane to afford 556 mg (44%) of **5** as a oil: ^{1}H NMR δ 2.41 (s, 3H), 2.74 (t, 2H), 2.95 (t, 2H), 3.64 (s, 3H). Anal. Calcd for $C_5H_{10}O_2S_2$: C, 36.12; H, 6.06; S, 38.57. Found: C, 36.25; H, 6.20; S, 38.57. Further elution afforded 400 mg of recovered **2**.

Method B. To a solution of 194 mg of **2** (0.816 mmol) in 2 mL of 1,2-dichloroethane at room temperature was added 70 μL of sulfuryl chloride (0.86 mmol), and the mixture was stirred for 5 min. To the resulting yellow solution was added 174 mg of sodium thiomethoxide (2.48 mmol). The resulting mixture was stirred for 1 h, the reaction was quenched with saturated aqueous ammonium chloride solution, and the mixture was extracted three times with ether. The organic phase was washed twice with water, dried over $MgSO_4$, and evaporated to a residue which was chromatographed on silica gel eluting with a 1:9 mixture of ether and hexane. Compound **5** was obtained (109 mg, 40%) as an oil, along with 92 mg of recovered **2**.

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