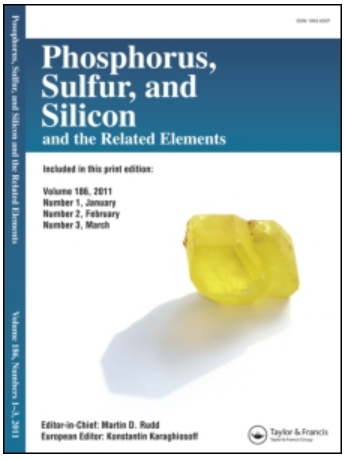

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WILLGERODT-KINDLER'S MICROWAVE-ENHANCED SYNTHESIS OF THIOAMIDE DERIVATIVES

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WILLGERODT-KINDLER'S MICROWAVE-ENHANCED SYNTHESIS OF THIOAMIDE DERIVATIVES

Jacques H. Poupaert,[a] *Sandro Duarte,*[a] *Evelina Colacino,*[a] *Patrick Depreux,*[b] *Christopher R. McCurdy,*[c] *and Didier L. Lambert*[a]
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The Willgerodt-Kindler reaction was applied to a series of aromatic aldehydes and ketones. The reactions were performed in a dipolar aprotic solvent (mainly DMF) in the presence of a base catalyst (4-methylmorpholine) and utilized microwave (mw) irradiation. The pulsed mw technique rather than the continuous irradiation was preferred because it limited side reactions and hydrogen sulfide production. While not always superior to the thermal activation of the reaction, the procedure involving repetitive short pulses of microwave irradiation was found to be faster and result in consistently cleaner products. The technique can be easily applied in a fast parallel synthesis process.

Keywords: Catalysis; microwave; sulfur; thioamide; Willgerodt-Kindler

INTRODUCTION

A recent study based on the analysis of a large virtual library constructed with frequently occurring pharmacophores in drug molecules concluded that amides incorporating a basic amine moiety constitute an interesting family of potentially CNS-active molecules amenable to combinatorial chemistry.[1] However, the therapeutic utility of amides is somewhat limited due to their extensive degradation in plasma, especially when the amide function is formulated in a peptide structure. One approach to increase the plasma half-life of such compounds is to

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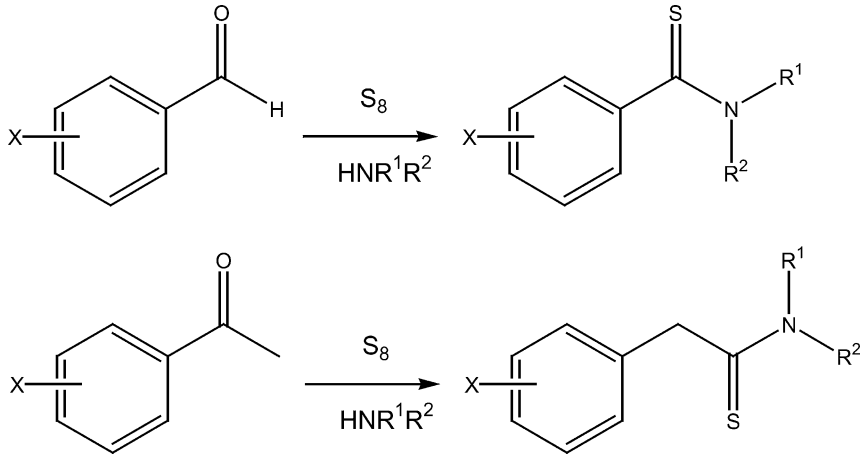
substitute one or more amide linkage(s) by thioamide linkage(s), a modification leading to improved metabolic resistance.[2] The thioamide NH is a stronger hydrogen bond donor than the amide NH, and the larger and less electronegative sulfur atom, relative to oxygen, is a weaker hydrogen bond acceptor.[3] These two factors combined may alter not only the hydrogen bonding ability at the receptor or enzyme level but also induce conformational changes and higher lipophilicity in the modified molecule.[4,5] As a result, the substitution of thioamides for amides appears to be a promising and productive tool in drug discovery and especially in the search for novel CNS-active drugs, with particular emphasis on generating compounds with improved capacity to cross physiological barriers, including the brain–blood barrier.[6]

The thiobenzamide moiety in particular appears to be an interesting pharmacophore in medicinal chemistry, with widespread applications including estrogen receptor antagonists,[7] antifungal[8] and antibacterial agents,[9] aldose reductase inhibitors,[10] etc. Access to thioamides is well documented in the literature.[11–13] For the construction of thioamides of pharmacological interest, the most employed method is based on the thionation of an amide precursor using P_4S_{10} or a variant such as Lawesson's reagent[14] or by means of a solid-supported thiophosphate.[15] The latter approach was used recently to synthesize a library of thioamide pharmacological probes. This method implies, however, the prior construction of the amide precursor.[16] In this connection, the Willgerodt-Kindler (WK) reaction offers a more convergent alternative to the above approach.[17]

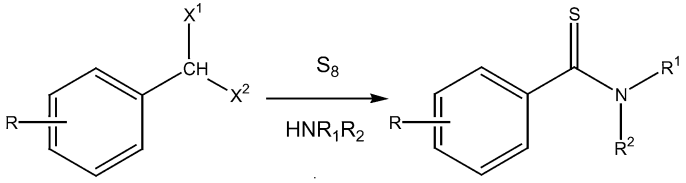
The WK reaction involves the reaction of an aldone (aldehyde or ketone), sulfur, and a primary or secondary amine to yield chiefly a thioamide derivative (Scheme 1).[18] When applied to an arylalkylketone,[19] this reaction behaves as an autoredox system in which the carbonyl of the ketone is reduced while the terminal methyl group of the alkyl side chain is oxidized.[20] The reaction can also be applied to aldehydes.[21] Sulfur has been also substituted by selenium.[22] It is noteworthy that the yield drops sharply when the number of methylenes linking the carbonyl to the terminal methyl group increases.[23,24] As a matter of fact, the reaction is useful only when the number of methylene groups is equal to 0–2.[25] Practically, the WK reaction with morpholine is used to transform acetophenones to phenylacetic acids via the intermediate phenylacetothiomorpholide, which is hydrolyzed either in acidic or basic solution to the desired acid.[26,27] One of the drawbacks of the reaction is that the amine itself is often partially oxidized by sulfur, and this in turn produces hydrogen sulfide. This is the reason for the popularity of morpholine as the amine partner, due precisely to its greater resistance to oxidation.[28]



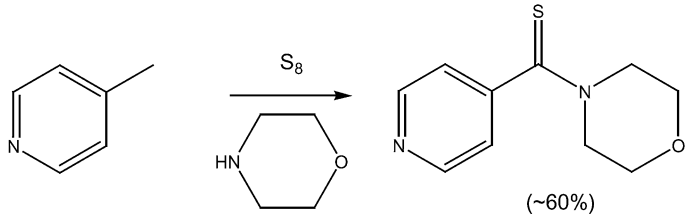
SCHEME 1 Willgerodt-Kindler (WK) synthesis of thioamides from an aromatic aldone (aldehyde or ketone) precursor.

While the Willgerodt-Kindler reaction has suffered in the past from a bad reputation, several recent developments have rendered the (WK) reaction a more attractive reaction to the medicinal chemist:

1. The reaction shows a high degree of tolerance as to the nature of the aryl precursor and amine, as illustrated in the Scheme 2 for benzylic



X_1 = Halide, CN, -NR_1R_2, OH, …; X_2 = H or X_1 = X_2 = Halide, = O, = N_2



SCHEME 2 WK synthesis of thiobenzamides from benzylic precursors.

substrates.[29–31] In the case of WK's synthesis of thiobenzamides, the aryl precursor can be either mono- or disubstituted on the benzylic carbon. The amine can be either primary or secondary.
2. The reaction can be improved when run in dipolar aprotic solvents such as DMF.
3. The reaction can also be improved when run in the presence of a basic catalyst such as triethylamine.[32]
4. Limited examples using simple arylalkylketones and morpholine showed the usefulness of microwave heating in the WK reaction.[33]

In this article, we report applications of the WK reaction to acetophenones implementing the improvements mentioned in points 2–4.

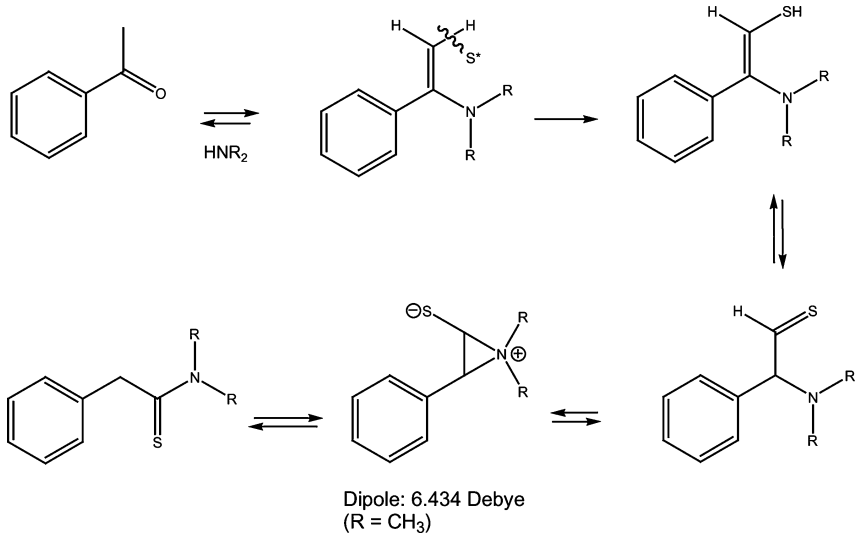
RESULTS AND DISCUSSION

During the first stage of this research, different attempts on simple model compounds showed the difficulty of applying the microwave technique to the WK reaction in spite of several anterior reports.[33–36] Reaction in neat phase with continuous irradiation led to black tar containing too many components to be effectively useful, and indeed Nooshabadi et al.[33] used column chromatography to purify the thiomorpholides.

Model substrates taken from previous publications or Vogel's textbook[18] were therefore selected as "benchmarks" to test the value of using microwave activation versus thermal heating. Improved "actual yields" obtained this way reflect practical improvements of the reaction, as the same straightforward recovery procedure was always applied during the course of this research (ethanol precipitation and recrystallization; for further details see the Experimental section below). Three procedures were compared, involving: (1) heating in neat phase a mixture of a benzaldehyde or acetophenone, sulfur, and morpholine (for the ratio of reagents and reaction conditions, see the Experimental section below) at 135°C; (2) same procedure as in (1), the reaction medium being diluted with equal volume of DMF and 4-methylmorpholine (4 MM); (3) same procedure as in (2), but applying pulsed microwave irradiation. The choice of 4 MM in (3) was motivated by its suitable boiling point and the fact that tertiary amines, while catalyzing the WK reaction, also undergo extensive thionation on the methylene vicinal to the basic nitrogen. This side reaction was minimized when using 4 MM.

Based on a tentative mechanism proposed earlier, it was concluded that the reaction, when applied to arylalkylketones, proceeds via an

aziridinium-thiolate betaine[37] intermediate possessing a high dipole moment (see the Experimental section below), which strongly suggested that the reaction was amenable to microwave (mw) enhancement (Scheme 3). The polar nature of this key intermediate was also consistent with the improvement of the yields observed when running the WK reaction in polar aprotic solvents such as DMF.[37]



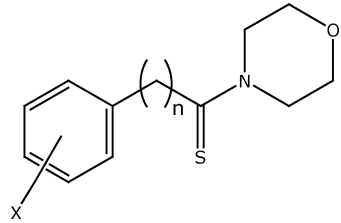
SCHEME 3 Proposal of mechanism for the WK reaction.

The pulse technique for mw irradiation was chosen for thermal equilibration, minimizing hydrogen sulfide production, which gives rise to side reactions.[21] Indeed, we noted that hydrogen sulfide production was strongly diminished when using mw compared to the thermal conditions in (1). The continuous irradiation process, especially in solvent-free conditions, led to complex product mixtures and, in agreement with a previous study,[37] the thiomorpholide had to be isolated by chromatographic techniques.

As is apparent from Table I, while not always superior to (2), procedure (3) was found to proceed faster and result in consistently cleaner products that were more easily purified. However, both methods (2) and (3) failed to give a solid material when applied to propiophenone.

The technique (3) can be easily applied in a fast parallel synthesis process. As was noted in previous publications,[37–39] benzaldehydes gave in general consistently higher yields than acetophenones. Moreover, when applying the mw method in (3), the time of reaction

TABLE I Structure and Yield of Thiomorpholides

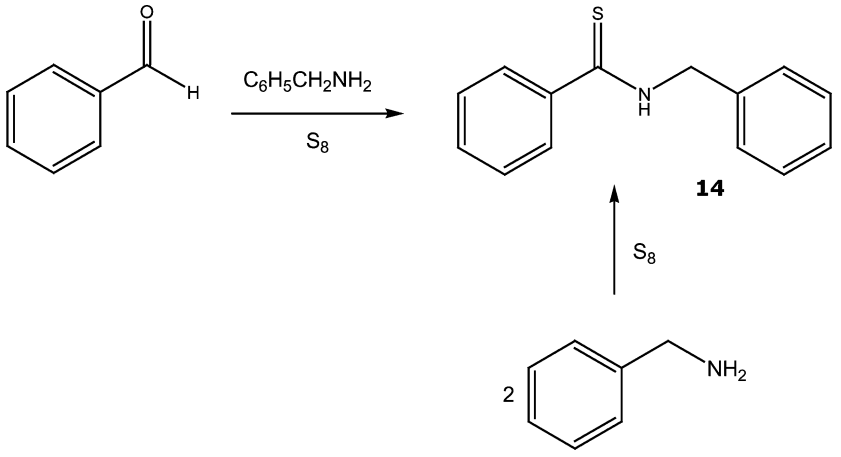


#	X	n	Yields (%)		
			Method (1)	Method (2)	Method (3)
1	H	0	85	83	85
2	4-OCH_3	0	83	87	85
3	4-OH	0	67	77	72
4	2-OH, 4-Cl	0	72	82	88
5	4-Br	0	73	83	79
6	4-$N(CH_3)_2$	0	87	92	86
7	H	1	51	67	65
8	4-CH_3	1	55	65	62
9	4-OCH_3	1	62	67	72
10	4-Cl	1	48	62	68
11	4-Br	1	50	58	62
12	4-C_6H_5	1	42	56	58
13	2-Acetylnaphtalene	1	62	70	72
15	CH_3CH_2	1	nd	nd	63
16	$CH_3CH_2CH_2$	1	nd	nd	43
17	$CH_3(CH_2)_3$	1	nd	nd	55
18	$CH_3(CH_2)_5$	1	nd	nd	49
19	$CH_3(CH_2)_7$	1	nd	nd	62
20	$CH_3CH_2CH(CH_3)$	1	nd	nd	35
21	$(CH_3)_2CH(CH_2)_2$	1	nd	nd	58
22	Tetrahydronaphthyl	1	nd	nd	61
23	Cyclohexyl	1	nd	nd	65
24	2-OH, 5-Cl	1	nd	nd	89

was considerably shorter for benzaldehydes than acetophenones. While 2 h was necessary for conversion of acetophenones, 30 min was sufficient for benzaldehydes. This approach therefore appears very attractive for the *N*-benzoylation of amines and compares favorably with *N*-thioacylphthalimides.[37]

When we tried to extend the mw technique to other amines, and especially benzylamine, we encountered a special problem in that when applying the recommendation of Nooshabadi et al.[33] regarding the molar ratio of reagents (ketone:sulfur:amine, 1:2:3) in the reaction of benzaldehyde with benzylamine, the actual yield was

superior to 100%! Closer examination of the literature revealed the benzylamine autocondenses in the presence of sulfur to produce *N*-thiobenzoylbenzylamine (Scheme 4). We have reproduced this reaction (see the Experimental section below). While it is a low-yield process, this indicates that especially when running the reaction under drastic temperature conditions (such as under continuous mw irradiation) and considerable excess of sulfur and amine, the extent of amine oxidation can produce high-yield impurities. As noted previously, sulfur excess also increase the generation of thiophene impurities.



SCHEME 4 WK reaction of benzaldehyde and benzylamine, and oxidative autocondensation of benzylamine in the presence of sulfur.

CONCLUSION

An interesting aspect associated with the combination of an aprotic polar solvent such as DMF, the use of a base catalyst resistant to sulfur oxidation, and microwave was the ease of recovery of the thiomorpholides along with the minimization of H_2S production. However, the yields were not substantially higher by the mw technique (3) than by the improved thermal method (2). Additionally, in view of the high yields and short reaction time when using the mw method (3), the WK reaction applied to benzaldehydes provides an efficient technique for benzoylation of amines. While this point was not addressed here, the mw technique can probably be easily applied in a fast parallel synthesis process.

EXPERIMENTAL

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 spectrometer using KBr pellets. Wave numbers are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker AC-300 spectrometer. Compounds were dissolved in DMSO-d6 or $CDCl_3$. Chemical shifts are expressed in the δ scale with TMS as internal standard. Thin layer chromatography analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). All the compounds reported here were routinely checked in two standard solvents: acetone/toluene/cyclohexane (solvent A, 5:2:3, *v/v/v*) and methanol/chloroform equilibrated with ammonia (solvent B, 1:9, *v/v*). High performance reverse-phase thin-layer chromatography conditions were: HPTLC plates RP-18 F-254 S (Merck), methanol:water (75/25, *v/v*). All compounds reported were found homogenous under such TLC and HPTLC conditions. All reagents were purchased from Aldrich. All solvents were of the A. C. S. reagent grade (Aldrich). Elemental analyses were obtained by courtesy of Prof. B. Masereel (FUNDP, Namur, Belgium). The microwave used for this study was a 750 W MX B-54 (2450 MHz) model. 4-Methylmorpholine (4 MM) was dried by refluxing over KOH for 1 h prior to distillation at atmospheric pressure. The preparation of **1** and **12** is representative of the synthesis of all other entries (see Table I). The isolation and purification procedure is quite similar to that employed by Rolfs and Liebscher in *Organic Syntheses*.

2-Phenyl-4-yl-1-morpholin-4-yl-ethanethione [(1, $C_{12}H_{15}NOS$), mw Condition (3)]

A mixture of 48.0 g (0.4 mol) of acetophenone, 12.8 g (0.4 mol) of sulfur, 72.0 g (0.82 mol) of morpholine and 25 ml of DMF was mixed thoroughly in a wide-bore 500 ml flask. The flask was placed on the rotating plateau of a microwave oven and irradiated according to the following scheme: after an initial pulse of 1 min at 750 W and 3.0 min rest, 25 pulses of 90 W of 1.5 min spaced out by 3.0 min were applied. During thermal equilibration after each pulse, the dark red reaction mixture was stirred. The hot reaction mixture was allowed to cool and was washed successively by 200 ml of distilled water, 200 ml of 0.1N HCl, 200 ml of brine, and 200 ml of distilled water. On standing at room temperature for 12 h, the oil crystallized. The solid material was triturated with 150 ml of absolute ethanol to discharge the dark red oily contaminant, and the suspension was left in a refrigerator overnight. The resulting

yellow powder was collected on a Büchner filter and washed with 125 ml of cold 1-chlorobutane. The air-dried powder was recrystallized from 600 ml of methanol to give 57.2 g (65% yield) of a yellow crystalline material, m.p. 77–79°C. On standing for 72 h, the methanol mother liquors deposited additional material (3.7 g, m.p. 75–78°C). Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.37 (m, 2H, H-5′), 3.61 (m, 2H, H-6′), 3.72 (m, 2H, H-2′), 4.34 (s, 2H, H-2), 4.25 (m, 2H, H-3′), 7.23 (m, 1H, ArH), 7.31 (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 50.06 (C-2), 50.50 (C-6′), 50.70 (C-3′), 65.99 (C-5′), 66.21 (C-2′), 127.01 (C-4″), 127.11 (C-3″), 127.66 (C-5″), 128.84 (C-2″ and C-6″), 135.70 (C-1″), 199.91 (C═S). Yield, 85%.

2-Biphenyl-4-yl-1-morpholin-4-yl-ethanethione [(12, $C_{18}H_{19}NOS$), Thermal Conditions (1) and (2)]

A mixture of 26.5 g (0.135 mol) of 4-acetylbiphenyl, 8.0 g (0.25 mol) of sulfur, and 40.0 g (0.46 mol) of morpholine was stirred and heated in an oil bath at 135°C for 6 h. The hot dark red reaction mixture was allowed to cool overnight. On standing at room temperature for 12 h, the oil solidified. This solid material was crystallized from 400 ml of absolute ethanol. Overnight cooling in a refrigerator produced yellow crystals, which were collected and washed twice with 125 ml of cold diethyl ether to yield 34.1 g of a yellow gray material. A second crystallization from 700 ml of absolute ethanol gave 19.76 g, m.p. 73–74°C, lit. 73–74°C. In method (2), 12.5 ml of DMF and 12.5 ml of 4 MM were added to the reaction medium. The other conditions were the same as above. The yield was 56%. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.44 (t, 2H, $J_{5'-6'} = 4.41$ Hz, H-5′), 3.67 (t, 2H, $J_{6'-5'} = 4.41$ Hz, H-6′), 3.75 (t, 2H, $J_{2'-3'} = 4.41$ Hz, H-2′), 4.37 (t, 2H, $J_{3'-2'} = 4.41$ Hz, H-3′), 4.39 (s, 2H, H-2), 7.32–7.52 (m, 9H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6) δ: 50.18 (C-2), 50.27 (C-6′), 50.85 (C-3′), 66.19 (C-5′), 66.38 (C-2′), 127.01 (C-4″), 127.46 (C-3″ and C-3‴), 127.65 (C-5″ and C-5‴), 128.24 (C-2″ and C-6″), 128.82 (C-2‴ and C-6‴), 134.90 (C-4‴), 140.14 (C-1‴), 198.52 (C═S). IR (cm^{-1}) 3032, 1609, 1495 (s), 1446, 1435, 1112 (s); MS, m/e (relative intensity) 221 (93), 188 (24), 134 (46), 130 (62), 91 (100), 86 (66).

2-Biphenyl-4-yl-1-morpholin-4-yl-ethanethione [(12, $C_{18}H_{19}NOS$), mw Condition (3)]

A mixture of 26.5 g (0.135 mol) of 4-acetylbiphenyl, 8.0 g (0.25 mol) of sulfur, 40.0 g (0.46 mol) of morpholine and 25 ml of DMF was placed on the rotating plateau of a microwave oven and irradiated according

to the following scheme: after an initial pulse of 1 min at 750 W and 3.0 min rest, 25 pulses of 90 W of 1.5 min spaced out by 3.0 min were applied. During thermal equilibration after each pulse, the dark red reaction mixture was stirred. The hot reaction mixture was allowed to cool overnight. On standing at room temperature for 12 h, the oil crystallized. The solid material was triturated with 150 ml of absolute ethanol to discharge the dark red oily contaminant, and the suspension was left in a refrigerator overnight. The resulting yellow powder was collected on a Büchner filter and washed with 125 ml of cold diethyl ether to give 28.1 g of rough material, which was recrystallized from 600 ml of absolute ethanol to give 25.0 g of a yellow crystalline material (m.p. 74–75°C). By reprocessing the mother liquors, an additional 2.4 g was obtained. The total yield was 27.39 g (58%). A lower yield (52%) was registered when 25 pulses of 30 s at 240 W were applied.

N-Thiobenzoylbenzylamine [(14, $C_{14}H_{13}NS$), Oxidative Self-Condensation]

A mixture of 80 g (74.6 mmol) of benzylamine and 40 g (124.7 mmol) of sulfur were stirred magnetically for 15 min at room temperature, during which time a reddish color soon developed and the smell of ammonia was noticed. The reaction mixture was then stirred and heated in an oil bath to 130°C for 2 h. Throughout the whole process, the flask was connected to a water aspirator to remove any hydrogen sulfide and ammonia formed during the reaction. After partial cooling, the reaction mixture was diluted with 250 ml of absolute ethanol and filtered to remove some unreacted sulfur by paper filtration. On cooling overnight, the filtrate deposited a yellow precipitate, which was collected on a filter, dried, and recrystallized from petroleum ether to give 24.8 g (29%) of the desired compound. m.p. 85–87°C. Rf = 0.45 (solvent A), 0.67 (solvent B). The reaction gave a modest 23% yield by the mw technique.

This material (entry **1**) was similar in all respects to that obtained by reacting benzaldehyde with benzylamine in the presence of sulfur (either by method (1) or method (3)). For method (3), 10 pulses of 240 W spaced out by 3 min were applied.

2-(4-Ethyl-phenyl)-1-morpholin-4-yl-ethanethione [(15, $C_{14}H_{19}NOS$), mw Condition (3)]

m.p. 92.3°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.24 (t, 3H, $J = 7.35$ Hz, CH_3), 2.69 (q, 2H, $J = 7.35$ Hz, $\underline{CH_2}CH_3$), 3.39 (t, 2H, $J_{5'-6'} = 4.41$ Hz, H-5′), 3.61 (t, 2H, $J_{6'-5'} = 4.41$ Hz, H-6′), 3.72

(t, 2H, $J_{2'-3'}$ = 4.41 Hz, H-2′), 4.31 (s, 2H, H-2), 4.34 (t, 2H, $J_{3'-2'}$ = 4.41 Hz, H-3′), 7.01–7.15 (m, 5H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 15.15 (CH_3), 27.87 ($\underline{CH_2}CH_3$), 50.18 (C-2), 50.40 (C-6′), 50.77 (C-3′), 66.12 (C-5′), 66.36 (C-2′), 127.81 (C-3″ and C-5″), 129.11 (C-2″ and C-6″), 134.88 (C-1″), 137.20 (C-4″), 199.98 (C=S). IR (cm^{-1}): 3084, 2966, 2851, 1603 (C=S), 1463, 1428. Yield, 63%.

2-(4-Propyl-phenyl)-1-morpholin-4-yl-ethanethione [(16, $C_{15}H_{21}NOS$), mw Condition (3)]

m.p. 90.2°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.89 (t, 3H, J = 7.35 Hz, CH_3), 1.64 (m, 2H, J = 7.35 Hz, $\underline{CH_2}CH_3$), 2.55 (t, 2H, J = 7.35 Hz, $\underline{CH_2}CH_2CH_3$), 3.37 (t, 2H, $J_{5'-6'}$ = 4.41 Hz, H-5′), 3.62 (t, 2H, $J_{6'-5'}$ = 4.41 Hz, H-6′), 3.71 (t, 2H, $J_{2'-3'}$ = 4.41 Hz, H-2′), 4.31 (s, 2H, H-2), 4.35 (t, 2H, $J_{3'-2'}$ = 4.41 Hz, H-3′), 7.09–7.23 (m, 4H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 13.89 (CH_3), 24.47 ($\underline{C}H_2CH_3$), 37.65 ($\underline{C}H_2CH_2CH_3$), 50.21 (C-2), 50.41 (C-6′), 50.79 (C-3′), 66.12 (C-5′), 66.38 (C-2′), 127.45 (C-3″ and C-5″), 129.01 (C-2″ and C-6″), 132.90 (C-1″), 141.88 (C-4″), 200.44 (C=S). IR (cm^{-1}): 3043, 2956, 1602, 1497, 1458, 1432 cm^{-1}. Yield, 43%.

2-(4-Butyl-phenyl)-1-morpholin-4-yl-ethanethione [(17, $C_{16}H_{23}NOS$), mw Condition (3)]

m.p. 94.2°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.93 (t, 3H, J = 7.35 Hz, $CH_2\underline{CH_3}$), 1.34 (m, 2H, $\underline{CH_2}CH_3$), 1.59 (m, 2H, $\underline{CH_2}CH_2CH_3$), 2.56 (t, 2H, J = 7.35 Hz, $\underline{CH_2}CH_2CH_2CH_3$), 3.38 (t, 2H, $J_{5'-6'}$ = 4.41 Hz, H-5′), 3.63 (t, 2H, $J_{6'-5'}$ = 4.41 Hz, H-6′), 3.70 (t, 2H, $J_{2'-3'}$ = 4.41 Hz, H-2′), 4.31 (s, 2H, H-2), 4.36 (t, 2H, $J_{3'-2'}$ = 4.41 Hz, H-3′), 7.09–7.23 (m, 5H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 13.91 (CH_3), 22.37 ($\underline{C}H_2CH-3$), 33.31 ($\underline{C}H_2CH_2CH_3$), 35.60 ($CH_2CH_2CH_2CH_3$), 50.20 (C-2), 50.39 (C-6′), 50.79 (C-3′), 66.12 (C-5′), 66.38 (C-2′) 128.36 (C-3″ and C-5″), 129.65 (C-2″ and C-6″), 133.02 (C-1″), 136.40 (C-4″), 140.89 (C-Ar), 200.35 (C=S). IR (cm^{-1}): 3051, 2921, 1609, 1497, 1459, 1439. Yield, 55%.

2-(4-Hexyl-phenyl)-1-morpholin-4-yl-ethanethione [(18, $C_{18}H_{27}NOS$), mw Condition (3)]

m.p. 86.3°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.87 (t, 3H, J = 7.35 Hz, CH_3), 1.29 [q, 6H, J = 7.35 Hz, $(\underline{CH_2})_3CH_3$], 1.58 [m, 2H, J = 7.35 Hz, $\underline{CH_2}(CH_2)_3CH_3$], 2.57 [t, 2H, J = 7.35 Hz, $\underline{CH_2}(CH_2)_4CH_3$], 3.38 (t, 2H, $J_{5'-6'}$ = 4.41 Hz, H-5′), 3.63 (t, 2H, $J_{6'-5'}$ = 4.41 Hz, H-6′), 3.73 (t, 2H, $J_{2'-3'}$ = 4.41 Hz, H-2′), 4.32 (s, 2H, H-2), 4.35

(t, 2H, $J_{3'-2'}$ = 4.41 Hz, H-3′), 7.11–7.26 (m, 4H, J = 7.35 Hz, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 14.10 (CH_3), 22.58 ($\underline{C}H_2CH_3$), 28.29 ($\underline{C}H_2CH_2CH_3$), 31.38 [$\underline{C}H_2(CH_2)_2CH_3$], 31.70 [$\underline{C}H_2(CH_2)_3CH_3$], 35.59 [$\underline{C}H_2(CH_2)_4CH_3$], 50.21 (C-2), 50.40 (C-6′), 50.79 (C-3′), 66.12 (C-5′), 66.38 (C-2′), 127.65 (C-3″ and C-5″), 129.01 (C-2‴ and C-6″), 132.89 (C-1″), 141.89 (C-4″), 200.44 (C=S). IR (cm^{-1}): 2956, 2921, 1605, 1512, 1486, 1433. Yield, 49%.

2-(4-Octyl-phenyl)-1-morpholin-4-yl-ethanethione [(19, $C_{20}H_{31}NOS$), mw Condition (3)]

m.p. 89.1°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.88 (t, 3H, J = 7.35 Hz, CH_3), 1.26 [pm, 10H, $(\underline{CH_2})_5CH_3$], 1.59 [t, 2H, J = 7.35 Hz, $\underline{CH_2}(CH_2)_5CH_3$], 2.57 (t, 2H J = 7.35 Hz, $\underline{CH_2}(CH_2)_6CH_3$), 3.40 (t, 2H, $J_{5'-6'}$ = 4.41 Hz, H-5′), 3.63 (t, 2H, $J_{6'-5'}$ = 4.41 Hz, H-6′), 3.73 (t, 2H, $J_{2'-3'}$ = 4.41 Hz, H-2′), 4.29 (s, 2H, H-2), 4.35 (t, 2H, $J_{3'-2'}$ = 4.41 Hz, H-3′), 7.12–7.23 (m, 4H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 14.03 (CH_3), 22.65 ($\underline{C}H_2CH_3$), 29.24 [$(\underline{C}H_2)_3(CH_2)_2CH_3$], 29.44 [$(\underline{C}H_2)_2(CH_2)_4CH_3$], 31.38 [$\underline{C}H_2(CH_2)_5CH_3$], 31.83 [$CH_2CH_2CH_3$], 35.52 [$\underline{C}H_2(CH_2)_6CH_3$], 50.34 (C-2′ and C-6′), 50.79 (C-2), 66.12 (C-3′), 66.32 (C-5′), 127.59 (C-3″ and C-5″), 128.95 (C-2″ and C-6″), 199.89 (C=S). IR (cm^{-1}): 2989, 2916, 1608, 1497, 1459, 1440. Yield, 62%.

2-[4-(2-Methyl-butyl)-phenyl]-1-morpholin-4-yl-ethanethione [(20, $C_{17}H_{25}NOS$), mw Condition (3)]

m.p. 117.0°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.81 (t, 3H, J = 7.35 Hz, $\underline{CH_3}CH_2$), 1.25 (d, 3H, J = 7.35 Hz, $\underline{CH_3}CH$), 1.61 (m, 2H, $CH_3\underline{CH_2}$), 2.53 (m, 1H, $CH_3\underline{CH}$), 3.38 (t, 2H, $J_{5'-6'}$ = 4.41 Hz, H-5′), 3.62 (t, 2H, $J_{6'-5'}$ = 4.41 Hz, H-6′), 3.72 (t, 2H, $J_{2'-3'}$ = 4.41 Hz, H-2′), 4.31 (s, 2H, H-2), 4.35 (t, 2H, $J_{3'-2'}$ = 4.41 Hz, H-3′), 7.09–7.25 (m, 4H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 12.16 ($\underline{C}H_3CH_2$), 21.61 ($\underline{C}H_3CH$), 30.92 ($\underline{C}H_2CH_3$), 42.31 ($\underline{C}H_2CH$), 50.20 (C-2), 50.33 (C-6′), 50.85 (C-3′), 66.24 (C-5′), 66.38 (C-2′), 127.59 (C-3″and C-5″), 129.44 (C-2″and C-6″), 133.48 (C-1″), 138.22 (C-4″), 200.31 (C=S). IR (cm^{-1}): 3082, 1603, 1485, 1462, 1434. Yield, 35%.

2-[4-(3-Methyl-butyl)-phenyl]-1-morpholin-4-yl-ethanethione [(21, $C_{17}H_{25}NOS$), mw Condition (3)]

m.p. 78°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.88 (d, 6H, J = 5.88 Hz, CH_3), 1.86 (m, 1H, CH), 2.45 (t, 2H, $\underline{CH_2}CH$), 3.39 (t, 2H,

$J_{5'-6'} = 4.41$ Hz, H-5′), 3.62 (t, 2H, $J_{6'-5'} = 4.41$ Hz, H-6′), 3.73 (t, 2H, $J_{2'-3'} = 4.41$ Hz, H-2′), 4.32 (s, 2H, H-2), 4,35 (t, 2H, $J_{3'-2'} = 4.41$ Hz, H-3′), 7.08–7.23 (m, 4H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 22.32 (CH_3), 30.15 (CH), 45.03 ($\underline{C}H_2CH$), 50.21 (C-2), 50,40 (C-6′) 50.78 (C-3′), 66.12 (C-5′), 66.38 (C-2′), 127.53 (C-3″ and C-5″), 129.66 (C-2″ and C-6″), 133.02 (C-1″), 140.59 (C-4″), 200.44 (C=S). IR (cm^{-1}): 3084, 1603, 1488, 1463, 1434. Yield, 58%.

1-Morpholin-4-yl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethanethione [(22, $C_{16}H_{21}NOS$), mw Condition (3)]

m.p. 111.8°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80 (t, 4H, $J = 5.88$ Hz, C-6″ and C-7″), 2.73 (t, 4H, C-5″ and C-8″), 3.44 (t, 2H, $J_{5'-6'} = 4.41$ Hz, H-5′), 3.65 (t, 2H, $J_{6'-5'} = 4.41$ Hz, H-6′), 3.74 (t, 2H, $J_{2'-3'} = 4.41$ Hz, H-2′), 4.27 (s, 2H, H-2), 4.35 (t, 2H, $J_{3'-2'} = 4.41$ Hz, H-3′), 6.99–7.03 (m, 3H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 23.16 ($2CH_2$), 29.05 (CH_2), 29.44 (CH_2), 50.21 (C-2), 50.34 (C-6′), 50.79 (C-3′), 66.25 (C-5′), 66.38 (C-2′), 124.87 (C-2″), 128.30 (C-3″ and C-9″), 129.59 (C-1″), 135.00 (C-4″), 137.75 (C-9″), 200.57 (C=S). IR (cm^{-1}): 2925, 2855, 1610, 1488, 1459, 1434. Yield, 61%.

2-(4-Cyclohexyl-phenyl)-1-morpholin-4-yl-ethanethione [(23, $C_{18}H_{25}NOS$), mw Condition (3)]

m.p. 107.1°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.38 (t, 6H, $J = 8.82$ Hz, H-3‴, H-4‴ and H-5‴), 1.76 (pt, 4H, $J = 7.35$ Hz, H-2‴ and H-6‴), 2.63 (m, 1H, $J = 7.35$ Hz, CH), 3.39 (t, 2H, $J_{6'-5'} = 4.41$ Hz, H-6′), 3.36 (t, 2H, $J_{5'-6'} = 4.41$ Hz, H-5′), 3.74 (t, 2H, $J_{2'-3'} = 4.41$ Hz, H-2′), 4.31 (s, 2H, H-2), 4.35 (t, 2H, $J_{3'-2'} = 4.41$ Hz, H-3′), 7.14–7.26 (m, 4H, ArH). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 26.14 (C-3‴ and C-5‴), 26.85 (C-4‴), 34.49 (C-2‴ and C-6‴), 44.19 (CH), 50.21 (C-2), 50.34 (C-6′), 50.85 (C-3′), 66.12 (C-5′), 66.38 (C-2′), 127.39 (C-3″ and C-5″), 127.71 (C-2″ and C-6″), 133.02 (C-1″), 147.06 (C-4″), 200.37 (C=S). IR (cm^{-1}): 3005, 2851, 1602, 1512, 1488, 1446. Yield, 65%.

(5-Chloro-2-hydroxy-phenyl)-morpholin-4-yl-ethanethione [(24, $C_{11}H_{12}ClNO_2S$), mw Condition (3)]

TLC system: CH_2Cl_2:AcOEt 80:20 v/v Rf = 0.7; m.p. 186–190°C. Spectral data: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.14 (S_{broad}, 1H, OH), 7.20 (d, 2 H, $J_{4-3} = 8.82$ Hz, H-4 and H-6), 6.84 (d, 1 H, $J_{4-3} = 8.82$ Hz, H-3), 4.25 (m, 2H, $J_{3'-2'} = 4.41$ Hz, H-3′), 3.73 (t, 2H, $J_{2'-3'} = 4.41$ Hz, H-2′), 3.58 (t, 2H, $J_{4'-5'} = 4.41$ Hz, H-4′), 3.46 (t, 2H, $J_{5'-4'} = 4.41$ Hz, H-5′); ^{13}C

NMR (300 MHz, DMSO-d_6) δ: 193.51 (C=S), 149.52 (C-2), 129.07 (C-6 and C-4), 127.78 (C-1), 122.34 (C-5), 117.10 (C-3), 65.86 (C-2′), 65.54 (C-5′), 51.56 (C-3′), 48.65 (C-4′). Yield, 89%.

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