Reductive Alkylation of Aromatic Amines with Enol Ethers

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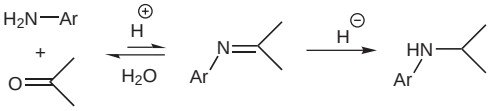
Dedicated to Professor A. Srikrishna on the occasion of his 50th birthday.

Abstract: Reductive alkylation of aromatic amines with 2-methoxypropene using 1.0 equivalent of HOAc and $NaBH(OAc)_3$ in 1,2-dichloroethane (DCE) at room temperature furnished *N*-isopropyl amines in 50–98% yields. This method was successfully extended to trimethylsilyl enol ethers. The mild reaction conditions provide a new alternative procedure for the reductive amination of electron deficient aromatic amines.

Key words: reductive alkylation, aromatic amines, 2-methoxypropene, trimethylsilylenol ethers, sodium triacetoxyborohydride

The amine group is regarded as one of the privileged functional groups in identifying novel lead compounds for drug discovery. Among the many methods available for the synthesis of secondary and tertiary amines, reductive amination, the reaction of a ketone or an aldehyde in the presence of an amine and a mild reducing agent,[2] is perhaps the most versatile. Although this method has been used for the preparation of a diverse range of amines, it often suffers from poor yields when applied to aromatic amines. Gribble and co-workers[3a] have first described for aromatic amines using $NaBH_4$–HOAc, later Abdel-Magid et al.[3b] has developed efficient procedure by simple modification of the reagent, $NaBH(OAc)_3$–HOAc.[3b] Apodaca et al. has used a catalytic amount of Bu_2SnCl_2 in combination with $PhSiH_3$[4] as reducing agent. These procedures have widely used for direct reductive amination of aromatic amines. Most importantly, these procedures are often low yielding and require longer reaction time with ketones despite using of excess reagents (up to 5 equiv).[3b] In the case of unreactive amines, the equilibrium is shifted to the left and excess carbonyl compounds will consume the reducing agent prior to the formation of the imine (Equation 1).[3b] To circumvent this problem, alternative stepwise procedure has been developed using stochiometric amount of $Ti(Oi\text{-}Pr)_4$ prior to adding reducing agent. Although, this modification has been effective and it has not been fully explored for electron deficient aromatic amines.[5,3b] Moreover, operationally not simple for large scale preparations. Recently, Park et al.[6] has reported one-pot reductive amination of acetals with aromatic amines using decaborane ($B_{10}H_{14}$) as the reducing agent. However, it is not compatible with reducible functional groups, e.g. ketones and basic amines.



Equation 1

In connection with an effort toward anti-hepatitis C (HCV) NS5B polymerase inhibitors, we required a safe and convenient procedure for the large scale preparation of methyl 3-(*N*-isopropyl)-amino-5-phenylthiophene-2-carboxylate (Figure 1), a pivotal intermediate to our target substructures.[7a] As the currently available methods to this intermediate were found to be inefficient and cumbersome, we have developed a simple, high-yielding modification to the standard reductive amination protocol, one that works particularly well for the preparation of N-alkylated aromatic amines.[3b]

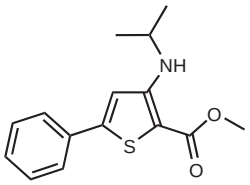
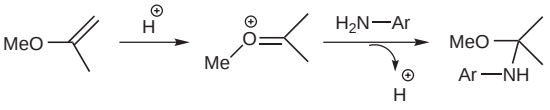


Figure 1

We have hypothesized that enol ethers/mild proton source could be used in place of ketones as no reducible groups are present (Equation 2) and do not require excess reagents. Moreover, the reaction rate is faster for addition of aromatic amines to an oxonium intermediate than to simple ketones. The highly reactive oxonium species is generated in situ by protonation of enol ethers.



Equation 2

We have chosen $NaBH(OAc)_3$ as our reducing agent as it offers mild reaction conditions, operational simplicity and avoids the use of toxic metals.[4] Reductive alkylation of 2-methoxypropene (5.0 equiv) using aniline with HOAc (2.0 equiv) and $NaBH(OAc)_3$ (3.0 equiv) in DCE at r.t. for one hour generated a inseparable 65:35 mixture of *N*-isopropylaniline and *N*,*N*-diisopropyl anilines. In contrast,

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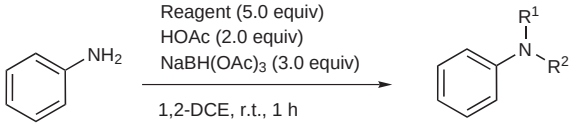
Table 1 Reactivity of Acetone Equivalents



2a: R^1 = H; R^2 = *i*-Pr
2b: R^1 = R^2 = *i*-Pr

Entry	Reagent	Product(s) (%)[a] (**2a**:**2b**)
1	2-Methoxypropene	65:35
2	Acetone	100:0
3	2,2-Dimethoxypropane	15:0[b]

[a] ^{1}H NMR ratio of crude products.
[b] Remaining is starting material.

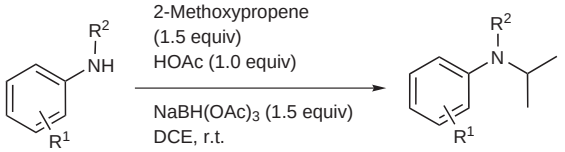
reaction with acetone gave *N*-isopropyl aniline as the sole product. Reductive alkylation with 2-methoxypropene is therefore much faster than with acetone and 2,2-dimethoxypropane[8] thus confirming our hypothesis (Table 1).

Reaction conditions were optimized for selective mono N-alkylation using aniline and 2-methoxypropene. Stochiometric amount of HOAc (1.0 equiv) is necessary for optimum yield and faster reaction although 20 mol% HOAc is sufficient. 1,2-Dichloroethane is solvent of choice compared to THF or CH_2Cl_2. Reductive alkylation of aniline (2.0 mmol) with 2- methoxypropene (2.0 mmol, 1.0 equiv), HOAc (1.0 equiv) and $NaBH(OAc)_3$ (3.0 mmol, 1.5 equiv) in DCE at room temperature for two hours provided *N*-isopropyl aniline in 96% isolated yield.

The generality of this method was examined with a variety of functionalized hindered unreactive anilines (Table 2). A wide range of anilines provided *N*-isopropyl anilines in good to excellent yields, including weakly nucleophilic and sterically hindered substrates (entries 1–3, 5 and 7). Small amount of dialkylated product was observed for electron rich anilines (entries 4 and 8). The reaction conditions are compatible with several functional groups, e.g. CN, NO_2, CO_2Et, I (Table 2). Good selectivity was obtained with reducible group such as COMe (entry 9). TFA can also be used instead of HOAc for unreactive anilines to facilitate the reaction rate (entry 12).

The methodology was also extended to trimethylsilyl (TMS) enol ethers in order to enhance the scope of the reaction, as many of TMS enol ethers are commercially available (Table 3) or easily prepared from the corre-

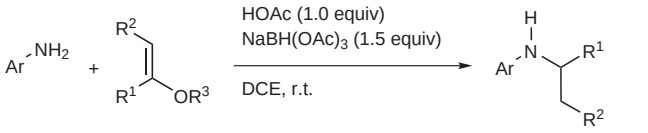
Table 2 Reductive Alkylation with 2-Methoxypropene

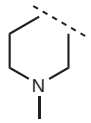
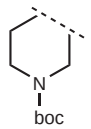
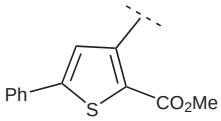
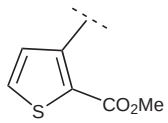


Entry[a]	R^1	R^2	Yield (%)[b]	Time (h)
1	*o*-CN	H	80	27
2	*o*-NO_2	H	65	45
3	*o*-CO_2Et	H	79	2.0
4	*o*-Me	H	97	3.0
5	*o*-*i*-Pr	H	98	3.0
6	*o*-F	H	96	3.0
7	*o*-I	H	80	3.0
8	*o*-OMe	H	98[c]	27
9	*m*-COMe	H	68	3.0
10	*p*-NO_2	H	92	20
11	2,4-Cl_2	H	83	2.0
12	H	Ph	50 77[d]	166 2.0

[a] Reaction scale 2.0 mmol.
[b] Isolated yield.
[c] Inseparable 8:1 mixture of mono- and diisopropyl anilines.
[d] TFA used instead of HOAc.

Table 3 Reductive Alkylation with TMS Enol Ether



Entry[a]	Ar	R^1	R^2	R^3	Yield (%)[b]	Time (h)
1	Ph	-$(CH_2)_4$-		TMS	78	2
2	Ph	-$(CH_2)_3$-		TMS	82	2
3	Ph	Ph	H	TMS	75	24
4[9]	Ph			TMS	65	2
5	Ph			TMS	0	96[c]
6		Me	H	Me	96 quant[d]	2
7		Me	H	Me	95	2

[a] Reaction scale 2.0 mmol.
[b] Isolated yield.
[c] Reaction is carried out at 67 °C.
[d] Reaction scale 20 mmol for overnight.

sponding ketones. Cycloalkanone TMS enol ethers also reacted with similar rate to 2-methoxypropene. Acetophenone TMS enol ether gave good yield as conventional reductive amination resulted in poor conversion.[3b] Enol ethers carrying a basic functionality were also good substrates (entry 4). Surprisingly, *N*-BOC piperidine failed to react even at high temperature and longer reaction time (entry 5). Unreactive heterocyclic amines also provided the desired N-alkylated products in excellent yields (entries 6 and 7). Reaction conditions are compatible with large scale preparation as it produced quantitative yield of methyl 3-(*N*-isopropyl)-amino-5-phenylthiophene-2-carboxylate (entry 6).

In summary, we describe a novel, and efficient method for the preparation of *N*-isopropyl aromatic amines[10] using 2-methoxypropene under reductive amination conditions. The methodology was also extended to commercially available trimethylsilyl enol ethers. Finally, it is a method of choice for reductive amination of weakly nucleophilic aromatic amines and sterically hindered unreactive carbonyl compounds.[11]

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(10) Few examples of preclinical drugs containing *N*-isopropyl aromatic amines: (a) HCV NS-3 protease inhibitor, **BILN-2061** (b) 5-HT-4 receptor antagonists, **LY353433** (c) 5-HT-4 agonists, **BIMU 8**.

(11) All new compounds were fully characterized (^{1}H NMR, ^{13}C NMR and HRMS) and exhibited spectroscopic data consistent with their structures. Yields refer to isolated and chromatographically pure compounds.

Typical Experimental Procedure.

To a stirred solution of anilines (2.0 mmol) in DCE (6.0 mL) under nitrogen was added sequentially 2-methoxypropene (0.287 mL, 3.0 mmol), HOAc (0.114 mL, 2.0 mmol) and $NaBH(OAc)_3$ (636 mg, 3.0 mmol). After stirring at r.t. for required time, then reaction mixture was quenched with aq 1 N NaOH solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Concentration of the extracts gave essentially pure product. However, the crude product was purified on small plug of silica gel using EtOAc–hexane mixture (1:20) as an eluent produced *N*-isopropylaromatic amine derivatives.

***N*-Isopropyl-aniline**:[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 8.2 Hz, 2 H), 6.66 (t, *J* = 7.2 Hz, 1 H), 6.58 (d, *J* = 8.2 Hz, 2 H), 3.90 (br s, 1 H), 3.63 (m, 1 H), 1.21 (d, *J* = 6.3 Hz, 6 H).

***N*,*N*-Diisopropylaniline**:[13]

2-(Isopropylamino)benzo-nitrile:[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 1 H), 7.37 (d, *J* = 7.5, 1 H), 6.68–6.60 (m, 2 H), 4.40 (br s, 1 H), 3.72 (m, 1 H), 1.26 (d, *J* = 6.4 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 134.4, 133.1, 118.3, 116.3, 111.2, 95.8, 44.3, 22.9.

***N*-Isopropyl-2-nitroaniline**:[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.6 Hz, 1 H), 8.02 (br s, 1 H), 7.42 (t, *J* = 8.5 Hz, 1 H), 6.86 (d, *J* = 8.9 Hz, 1 H), 6.61 (d, *J* = 8.2 Hz, 1 H), 3.84 (m, 1 H), 1.34 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 136.4, 132.0, 127.3, 115.1, 114.4, 44.1, 22.9.

Ethyl 2-(isopropylamino)benzoate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.1 Hz, 1 H), 7.76 (br s, 1 H), 7.35 (t, *J* = 8.5 Hz, 1 H), 6.74 (d, *J* = 8.6 Hz, 1 H), 6.58 (t, *J* = 7.5 Hz, 1 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 3.72 (br s, 1 H), 1.38 (t, *J* = 7.0 Hz, 3 H), 1.28 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 150.7, 134.7, 132.0, 114.2, 111.9, 110.1, 60.4, 43.5, 23.0, 14.6. HRMS (FAB$^+$): *m*/*z* calcd for $C_{12}H_{17}NO_2$ $[M + H]^+$: 208.1338; found: 208.1324.

***N*-Isopropyl-2-methylaniline**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (dt, *J* = 1.6, 7.2 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.64–6.60 (m, 2 H), 3.70–3.66 (m, 1 H), 3.30 (br s, 1 H), 2.12 (s, 3 H), 1.25 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 130.5, 127.3, 121.9, 116.6, 110.5, 44.2, 23.5, 17.8. HRMS (FAB$^+$): *m*/*z* calcd for $C_{10}H_{15}N$ $[M + H]^+$: 150.1283; found: 150.1283.

***N*,2-Diisopropylaniline**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.08 (m, 2 H), 6.70 (t, *J* = 7.3 Hz, 1 H), 6.66 (d, *J* = 7.9 Hz, 1 H), 3.72–3.66 (m, 1 H), 3.48 (br s, 1 H), 2.87–2.80 (m, 1 H), 1.25 (d, *J* = 6.7 Hz, 6 H), 1.24 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 132.2, 127.0, 125.3, 117.0, 111.4, 44.4, 27.4, 23.5, 22.6. HRMS (FAB$^+$): *m*/*z* calcd for $C_{12}H_{19}N$ $[M + H]^+$: 178.1596; found: 178.1596.

(2-Fluorophenyl)-isopropylamine: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.92 (m, 2 H), 6.70 (dt, *J* = 8.4, 1.6 Hz, 1 H), 6.62–6.56 (m, 1 H), 3.70 (br s, 1 H), 3.67–3.61 (m, 1 H), 1.24 (d, *J* = 6.2 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8 (d, *J* = 239 Hz), 136.2, 124.8, 116.3 (d, *J* = 7.6 Hz), 114.7 (d, *J* = 19.1 Hz), 112.8, 44.3, 23.2. HRMS (FAB$^+$): *m*/*z* calcd for $C_9H_{12}NF$ [M + H]$^+$: 154.1032; found: 154.1032.

(2-Iodophenyl)-isopropylamine: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.8 Hz, 1 H), 7.19 (t, *J* = 8.2 Hz, 1 H), 6.60 (d, *J* = 8.1 Hz, 1 H), 6.42 (t, *J* = 7.5 Hz, 1 H), 3.68–3.65 (m, 1 H), 1.26 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 139.4, 129.6, 118.4, 111.4, 86.1, 44.9, 23.2. HRMS (FAB$^+$): *m*/*z* calcd for $C_9H_{12}NI$ [M + H]$^+$: 262.0094; found: 262.0093.

***N*-Isopropyl-2-methoxyaniline**:[16] ^{1}H NMR (400 MHz, $CDCl_3$, 8:1): δ = 6.86 (dt, *J* = 7.6, 1.5 Hz, 1 H), 6.76 (dd, *J* = 7.8, 1.3 Hz, 1 H), 6.66–6.60 (m, 2 H), 4.05 (br s, 1 H), 3.84 (s, 3 H), 3.65–6.59 (m, 1 H), 1.24 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 137.6, 121.5, 116.1, 110.5, 109.7, 55.6, 44.0, 23.3.

1-[3-(Isopropylamino)phenyl]-ethanone: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 2 H), 7.21–7.18 (m, 1 H), 6.83–6.79 (m, 1 H), 3.72–3.66 (m, 1 H), 2.56 (s, 3 H), 1.23 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.0, 147.9, 138.4, 129.6, 118.2, 117.6, 112.2, 44.4, 27.0, 23.1. HRMS (FAB$^+$): *m*/*z* calcd for $C_{11}H_{15}NO$ [M + H]$^+$: 178.1231; found: 178.1232.

***N*-Isopropyl-4-nitroaniline**:[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 9.1 Hz, 2 H), 6.50 (d, *J* = 8.8 Hz, 2 H), 4.40 (br s, 1 H), 3.74–3.71 (m, 1 H), 1.27 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 137.6, 126.8, 111.5, 44.5, 22.7.

(2,4-Dichlorophenyl)-isopropylamine: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 1 H), 7.09 (m, 1 H), 6.61 (d, *J* = 8.8 Hz, 1 H), 3.64–3.61 (m, 1 H), 1.25 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.0, 127.9, 126.7, 119.6, 118.4, 111.3, 43.4, 21.8. HRMS (FAB$^+$): *m*/*z* calcd for $C_9H_{11}NCl_2$ [M + H]$^+$: 204.0348; found: 204.0347.

***N*-Isopropyl-*N*-phenylaniline**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 4 H), 6.99 (t, *J* = 7.3 Hz, 2 H), 6.87–6.85 (m, 4 H), 4.37–4.30 (m, 1 H), 1.16 (d, *J* = 6.6 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 129.4, 123.1, 121.8, 48.0, 21.3. HRMS (FAB$^+$): *m*/*z* calcd for $C_{15}H_{17}N$ [M + H]$^+$: 212.1440; found: 212.1439.

***N*-Cyclohexylaniline**:[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 8.4 Hz, 2 H), 6.67 (t, *J* = 7.5 Hz, 1 H), 6.61 (d, *J* = 8.1 Hz, 2 H), 3.28–3.23 (m, 1 H), 2.07–2.04 (m, 2 H), 1.80–1.10 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 129.5, 117.2, 113.5, 52.0, 33.7, 26.2, 25.3.

***N*-Cyclopentylaniline**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (m, 2 H), 6.68 (t, *J* = 2.1 Hz, 1 H), 6.61 (dd, *J* = 8.6, 1.0 Hz, 2 H), 3.82–3.67 (m, 2 H), 2.06–1.98 (m, 2 H), 1.76–1.43 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 129.4, 117.1, 113.4, 54.9, 33.8, 24.3. HRMS (FAB$^+$): *m*/*z* calcd for $C_{11}H_{15}N$ [M + H]$^+$: 162.1283; found: 162.1283.

***N*-(1-Phenylethyl)aniline**:[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 5 H), 7.11–7.07 (m, 2 H), 6.66 (t, *J* = 7.5 Hz, 1 H), 6.53 (d, *J* = 7.9 Hz, 2 H), 4.49 (q, *J* = 6.7 Hz, 1 H), 1.53 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 145.6, 129.4, 129.0, 127.2, 126.2, 117.6, 113.6, 53.8, 25.4.

1-Methyl-*N*-phenylpiperidin-4-amine: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.14 (m, 2 H), 6.68 (dt, *J* = 7.3, 1.0 Hz, 1 H), 6.61–6.58 (m, 2 H), 3.49 (br s, 1 H), 3.29 (br s, 1 H), 2.82 (m, 2 H), 2.31 (s, 3 H), 2.17–2.05 (m, 4 H), 1.54–1.46 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 129.5, 117.5, 113.5, 55.0, 47.5, 33.5. HRMS (FAB$^+$): *m*/*z* calcd for $C_{12}H_{18}N_2$ [M + H]$^+$: 191.1548; found: 191.1548.

Methyl 3-(Isopropyl-amino)-5-phenylthiophene-2-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 2 H), 7.43–7.34 (m, 3 H), 6.86 (s, 1 H), 6.71 (br s, 1 H), 3.83 (s, 3 H), 3.78–3.74 (m, 1 H), 1.29 (d, *J* = 6.4 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 155.8, 149.8, 133.7, 129.0, 126.1, 112.2, 97.4, 51.0, 46.3, 43.5, 23.5. HRMS (FAB$^+$): *m*/*z* calcd for $C_{15}H_{17}NO_2S$ [M + H]$^+$: 276.1059; found: 276.1059.

Methyl 3-(Isopropyl-amino)thiophene-2-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 5.6 Hz, 1 H), 6.69 (d, *J* = 5.4 Hz, 1 H), 3.84 (s, 3 H), 3.73–3.67 (m, 1 H), 1.28 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 155.5, 98.0, 132.4, 116.4, 51.0, 46.3, 23.5. HRMS (FAB$^+$): *m*/*z* calcd for $C_9H_{13}NO_2S$ [M + H]$^+$: 200.0745; found: 200.0745

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