Synthetic Equivalents Based on Weinreb Amide Functionality for Convenient Access to Monoprotected α-Diketones

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Abstract: A convenient new strategy for the synthesis of monoprotected α-diketones has been achieved. The strategy is based on the use of hitherto unreported *N*-methoxy-*N*-methyl-1,3-dithiolane-2-carboxamide and *N*-methoxy-*N*-methyl-1,3-dithiane-2-carboxamide as synthetic equivalent for an α-dicarbonyl unit with opposing polarity. Nucleophilic addition on the amide functionality followed by alkylation furnished the targeted monoprotected α-diketones in moderate to good yields.

Key words: dithiolanes, dithianes, α-diketones, Weinreb amide

The chemistry of α-diketones has been the subject of intense research efforts. Undoubtedly this is due to their synthetic potential and numerous applications associated with their chemistry.[1] Among the various synthetic methodologies available in the literature for the synthesis of α-diketones,[2] three approaches invoke the use of 1,2-dicarbonyl equivalents. All the three synthetic equivalents, Mitchell's 1,2-di (1*H*-imid-azol-1-yl)ethane-1,2-dione,[3] Westhoff's 1,4-dimethyl piperazine-2,3-dione,[4] and Sibi's *N*′,*N*″-dimethoxy-*N*′,*N*″-dimethylethanediamide,[5] used in these approaches are potential equivalents for the synthon **A** wherein both the carbonyls retain their normal polarity. To our surprise, there exists no synthetic equivalent in the literature for synthon **B** wherein one carbonyl retains its normal polarity and the other is umpoled and has been used for arriving at monoprotected α-diketones.[6] This would be of great interest and importance, not only for indirect synthesis of α-diketones, but more importantly for direct access to monoprotected α-diketones. Given the fact that monoprotected α-diketones have enjoyed equally pronounced attention as α-diketones and their obtainment from α-diketones especially by way of regiospecific acetalization has been problematic and scarce,[7] their ready access based on this new approach appeared promising and attractive for exploration. With this background, we envisaged **1** and **2** as potential equivalents for synthon **B** which could pave a way for an efficient route for monothioacetals of α-diketones **C** (Figure 1). The proposal is based on the increasing confidence that *N*-methoxy-*N*-methyl amides, popularly known as Weinreb amides,[8] are robust carbonyl equivalents and are being used industrially on multigram scale.[9] Surprisingly, both the proposed new compounds **1** and **2** are hitherto unreported in the literature. Presented herein are the results of this study.

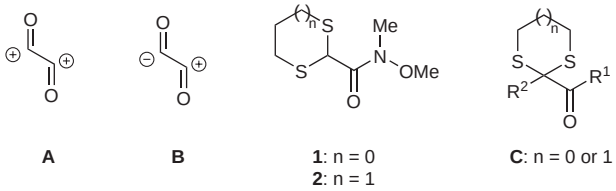
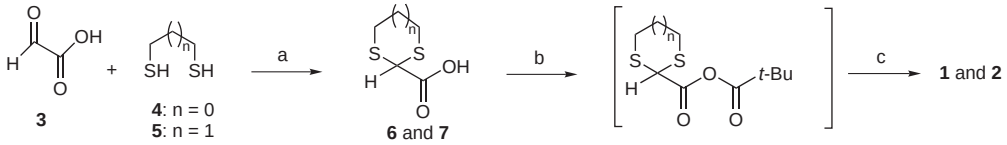


Figure 1

Analytically pure reagents **1** and **2** can be easily prepared on a five-gram scale in 75% and 70% yields from **6**[10] and **7**,[11] respectively, through the activation of the carboxyl group by mixed anhydride approach wherein the carboxyl carbon differ sterically[12] (Scheme 1).

Theoretically, two approaches differing in the sequencing of the reactions (i) alkylation at C-2 position in dithiolane or dithiane ring and (ii) addition of organometallic reagent to the amide carbonyl in **1** or **2** are possible for the obtainment of monoprotected α-diketones **C** (Scheme 2). Our initial attempts of direct alkylation at C-2 position in



Scheme 1 *Reagents and conditions*: (a) ethane-1,2-dithiol (1.1 equiv) for **6** (n = 0); propane-1,3-dithiol (1.1 equiv) for **7** (n = 1), 1 mol% PTSA, reflux, 8 h, 62% and 60%, respectively; (b) $(Me)_3CCOCl$ (1.1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C, 1 h; (C) MeONHMe·HCl (1.1 equiv), Et_3N (2.1 equiv), CH_2Cl_2, 0 °C, 1 h, 75% and 70% for **1** and **2**, respectively.

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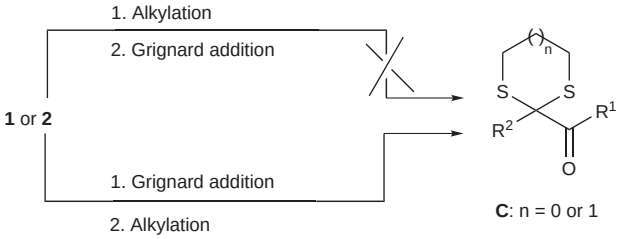
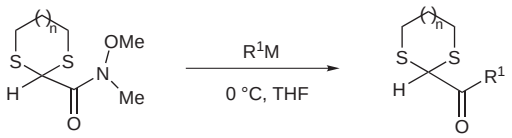
amides **1** and **2**, using LDA or NaH as a base and *n*-butylbromide as representative halide, led to extensive decomposition or partial recovery of the starting material. However, in sharp contrast, addition of various organometallic reagents, R^1MgBr and lithium acetylides (Table 1) on amides **1** and **2**, were successful and furnished 2-acyldithiolanes **8** and 2-acyldithiane **9**, respectively, in good yields. In context of yields, dithiolane amide **1** was particularly more attractive than dithiane amide **2**. Hence, for the remaining part of the study, we chose to use dithiolane amide **1** alone.



Scheme 2

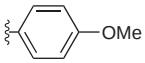
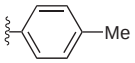
The sodium enolate **10** obtained from 2-acyldithiolane **8a–c** and **8e–g**, using NaH in DMF at 0 °C underwent clean alkylation at the C-2 position with varied alkyl halides furnishing the monoprotected α-diketones **11**–**25** in yields ranging from 58–75% (Table 2). However, in two isolated cases, O-alkylation was observed under these reaction conditions. The sodium enolate from **8d** (R^1 = phenyl) and **8h** (R^1 = 1-heptynyl) on reaction with *n*-butylbromide and ethyl-2-bromoacetate, respectively, gave exclusively the corresponding O-alkylated product **26** and **27**, respectively. This was evident from the absence of carbonyl stretching absorption in IR spectrum and presence of $–OCH_2–$ residue at δ = 3.58 ppm (t, *J* = 6.4 Hz) for compound **26** and δ = 4.62 ppm (s) for compound **27**. The typical structures are shown in Figure 2.

Table 1 Addition of Various Organometallic Reagents to Weinreb Amide **1** and **2**



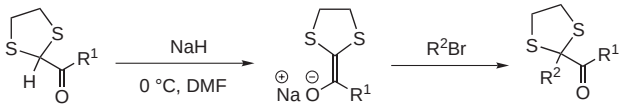
1: n = 0
2: n = 1

8: n = 0
9: n = 1

Entry	R^1M	Product	R^1	Yield (%)[a]
1	*n*-BuMgBr	**8a**	*n*-Bu	90
2	*n*-OctylMgBr	**8b**	*n*-Octyl	88
3	$THPO(CH_2)_4MgBr$	**8c**	$(CH_2)_4OTHP$	85
4	PhMgBr	**8d**[13]	Ph	90
5	$4\text{-}MeOC_6H_4MgBr$	**8e**		74
6	$4\text{-}MeC_6H_4MgBr$	**8f**		70
7	2-ThienylMgBr	**8g**	2-Thienyl	72
8	$Me(CH_2)_4C{\equiv}CLi$	**8h**	$C{\equiv}C(CH_2)_4Me$	75
9	*n*-BuMgBr	**9a**[14]	*n*-Bu	45
10	PhMgBr	**9b**[15]	Ph	50

[a] Yield of isolated product after flash chromatography. Spectral data of compounds **8d**, **9a**,**b** matched with literature data. All isolated new compounds[16] exhibited satisfactory analytical and spectral data.

Table 2 Alkylations of 2-Acyldithiolanes **8a–g** with Various Alkyl Halides



8 **10** **11–25**

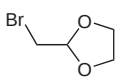
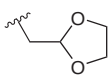
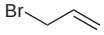
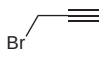
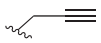
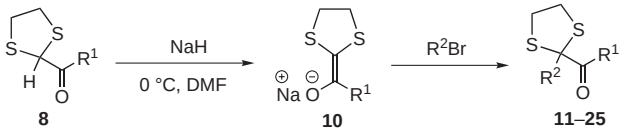
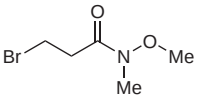
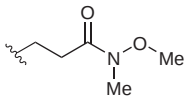
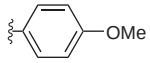
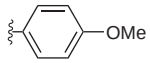
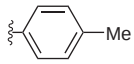
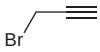
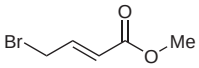
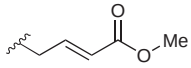
Entry	Starting substrate 2-acyldithiolane	R^2X	Product	R^1	R^2	Yield (%)[a]
1	**8a**	MeI	**11**	*n*-Bu	Me	70[17]
		BnBr	**12**	*n*-Bu	Bn	65
			**13**	*n*-Bu		58
			**14**	*n*-Bu		65
			**15**	*n*-Bu		72
2	**8b**	MeI	**16**	*n*-octyl	Me	68
		$BrCH_2COOEt$	**17**	*n*-octyl	CH_2COOEt	62
3	**8c**	*n*-BuBr	**18**	$(CH_2)_4OTHP$	*n*-Bu	73

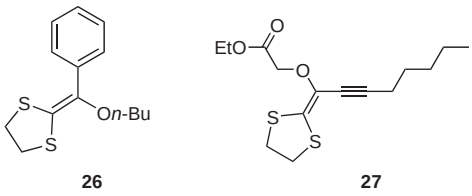
Table 2 Alkylations of 2-Acyldithiolanes **8a–g** with Various Alkyl Halides (continued)



8 **10** **11–25**

Entry	Starting substrate 2-acyldithiolane	R^2X	Product	R^1	R^2	Yield (%)[a]
4	**8d**		**19**	Ph		72
			**20**	Ph		70
5	**8e**	BnBr	**21**		Bn	69
		$BrCH_2COOEt$	**22**		CH_2COOEt	75
6	**8f**	$BrCH_2CH_2COOMe$	**23**		CH_2CH_2COOMe	54
7	**8g**		**24**	2-Thienyl		68
			**25**	2-Thienyl		62

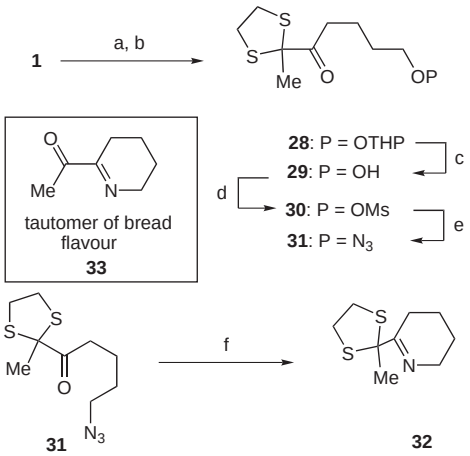
[a] Isolated yields after chromatography. New compounds[18] exhibited satisfactory analytical and spectral data.



26 **27**

Figure 2

As an interesting application of this new protocol for monoprotected α-diketones, we have successfully synthesized 6-(2-methyl-1,3-dithiolan-2-yl)-2,3,4,5-tetrahydropyridine **32**, a dithioacetal-protected derivative of an important target molecule **33**. The compound **33**, 6-acetyl-1,2,3,4-tetrahydropyridine[19] along with its enamine tautomer are key substances responsible for aroma of bread and is of great practical interest as an additive in food industry. The requisite carbon skeleton to arrive at compound **32** could be easily assembled in good yields by nucleophilic addition of $THPO(CH_2)_4MgBr$[20] on **1** followed by methylation at C_2-position to furnish **28**. Hydrolytic cleavage of THPO acetal and subsequent mesylation of free hydroxy group and displacement with azide afforded the azidoketone **31** as the key intermediate. Phosphine-mediated reductive cyclization furnished the proposed target **32** illustrating the usefulness of the developed method for monoprotected α-diketones (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) $THPO(CH_2)_4MgBr$ (3 equiv), THF, 0 °C, 85%; (b) NaH (1.1 equiv), MeI (1.2 equiv), DMF, 0 °C, 75%; (c) 10% PTSA, MeOH–H_2O (9:1), r.t., 6 h; (d) MsCl (1.5 equiv), pyridine (1.5 equiv), CH_2Cl_2, 0 °C to r.t., 4 h; (e) NaN_3 (1.2 equiv), DMF, 3 h, 78%; (f) PPh_3 (1.2 equiv), THF, reflux, 6 h, 80%.

To conclude, new synthetic equivalent based on Weinreb amide functionality has been realized and successfully utilized to synthesize variety of monoprotected α-diketones in moderate to good yields. The method is amenable for further exploitation according to the need and objectives of the synthetic endeavors. Synthetic equivalent **1** being a solid with indefinite shelf-life makes it advantageous for its convenient storage.

Acknowledgment

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(16) ***N*-Methoxy-*N*-methyl-1,3-dithiolane-2-carboxamide (1)**
Yield 75%; R_f = 0.35 (hexane–EtOAc, 8:2), colorless solid, mp 58–59 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.21 (s, 3 H), 3.30–3.33 (m, 2 H), 3.46–3.49 (m, 2 H), 3.76 (s, 3 H), 5.36 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.9, 38.7, 47.9, 61.5, 171.4. IR ($CHCl_3$): 2752, 1674, 1451, 1378, 1242 cm^{-1}. Anal. Calcd for $C_6H_{11}NO_2S_2$: C, 37.28; H, 5.74; N, 7.25; S,33.18. Found: C, 37.11; H, 5.63; N, 7.31; S, 3310. HRMS (EI): *m/z* calcd for $C_6H_{12}NO_2S_2$ [M + H]$^+$: 194.0309; found: 194.0304.
***N*-Methoxy-*N*-methyl-1,3-dithiane-2-carboxamide (2)**
Yield 70%; R_f = 0.30 (hexane–EtOAc, 8:2), colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96–2.10 (m, 2 H), 2.49–2.55 (m, 2 H), 3.16 (s, 3 H), 3.50 (m, 2 H), 3.68 (s, 3 H), 4.64 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 25.6, 31.9, 34.8, 61.2, 170.5. IR ($CHCl_3$): 2966, 1655, 1458, 1421, 1376, 1172 cm^{-1}. HRMS (EI): *m/z* calcd for $C_7H_{14}NO_2S_2$ [M + H]$^+$: 208.0466; found: 208.0467.
General Procedure for the Addition of Organometallic Reagent to *N*-Methoxy-*N*-methyl-1,3-dithiolane-2-carboxamide (1) and *N*-Methoxy-*N*-methyl-1,3-dithiane-2-carboxamide (2)
To a stirred solution of **1** or **2** (5 mmol) in 20 mL of anhyd THF, the appropriate solution of organometallic reagent (15 mmol) in 15 mL of anhyd THF was added under inert atmosphere at 0 °C and the mixture was stirred for 2 h. Subsequent hydrolysis was achieved by cautious addition of sat. NH_4Cl solution. Aqueous layer was extracted with EtOAc, dried over Na_2SO_4 and concentrated to get crude product, which was purified by column chromatography using (hexane–EtOAc, 90:10) to afford 1,3-dithiolane ketones **8** and 1,3-dithiane ketones **9**.
1-(1,3-Dithiolan-2-yl)nonan-1-one (8b)
Yield 88%; R_f = 0.50 (hexane–EtOAc, 9:1), colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, *J* = 7.2 Hz), 1.26–1.31 (m, 10 H), 1.59–1.63 (m, 2 H), 2.63 (t, 2 H, *J* = 7.2 Hz), 3.36–3.49 (m, 4 H), 4.80 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.7, 24.2, 29.1, 29.2, 29.4, 31.9, 38.5, 38.9, 57.2, 203.1. IR ($CHCl_3$): 2966, 1704, 1450, 1370 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{12}H_{22}OS_2Na$ [M + Na]$^+$: 269.1010; found: 269.1008.
1-(1,3-Dithiolan-2-yl)-5-(tetrahydro-2*H*-pyran-2-yloxy)pentan-1-one (8c)
Yield 85%; R_f = 0.4 (hexane–EtOAc, 8.5:1.5), colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48–1.80 (m, 4 H), 2.10–2.24 (m, 6 H), 2.74 (t, 2 H, *J* = 7.2 Hz), 3.31–3.37 (m, 4 H), 3.68–3.75 (m, 4 H), 4.57 (m, 1 H), 4.86 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 25.1, 27.1, 29.5, 29.8, 39.8, 40.1, 46.6, 62.3, 66.4, 98.8, 204.1. IR ($CHCl_3$): 2941, 1710, 1444, 1255, 1153 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{13}H_{22}O_3S_2Na$ [M + Na]$^+$: 313.0908; found: 313.0905.
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(18) **General Procedure for Alkylating 1,3-Dithiolane Ketones 8a–h with Various Alkyl Halides Leading to Monoprotected α-Diketones**
To a suspension of paraffin removed NaH (1.5 mmol) in 2 mL anhyd DMF at 0 °C, was added 1,3-dithiolane ketone **8** (1 mmol) in 5 mL of anhyd DMF followed by appropriate electrophile (1.2 mmol). The reaction mixture was stirred at 0 °C for 2 h and the excess NaH was cautiously quenched using 20 mL of sat. NH_4Cl solution at 0 °C. The reaction mixture was extracted three times using 25 mL of EtOAc. The organic layers were combined and given H_2O wash followed by brine wash and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the crude compound was purified by column chromatography (hexane–EtOAc) to afford monoprotected α-diketones. Representative spectral data for selected compounds are given below.
1-{2-[(1,3-dioxolan-2-yl)methyl]-1,3-dithiolan-2-yl}pentan-1-one (13)
Yield 58%; R_f = 0.45 (hexane–EtOAc, 8:2), colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, *J* = 7.1 Hz), 1.21–1.27 (m, 2 H), 1.46–1.50 (m, 2 H), 2.22 (t, 2 H, *J* = 7.1 Hz), 3.01 (d, 2 H, *J* = 7.1 Hz), 3.31–3.40 (m, 4 H), 3.95–4.15 (m, 4 H), 5.14 (t, 1 H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 22.1, 25.5, 38.6, 39.5, 40.7, 64.3, 74.8, 95.1, 201.1. IR ($CHCl_3$): 2927, 1712, 1450, 1375, 1255 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_3S_2$: C, 52.14; H, 7.29; S, 23.20. Found: C, 52.21; H, 7.52; S, 23.12.
1-(2-Allyl-1,3-dithiolan-2-yl)pentan-1-one (14)
Yield 65%; R_f = 0.6 (hexane–EtOAc, 9:1), colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, 3 H, *J* = 7.2 Hz), 1.18–1.29 (m, 2 H), 1.49–1.56 (m, 2 H), 2.70 (t, 2 H, *J* = 7.2

Hz), 2.81–2.83 (d, 2 H, *J* = 7.2 Hz), 3.24–3.35 (m, 4 H), 5.04–5.11 (m, 2 H), 5.67–5.76 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.2, 27.1, 37.1, 40.6, 44.0, 74.2, 119.0, 133.9, 205.1. IR ($CHCl_3$): 2956, 1698, 1425, 1304 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{11}H_{19}OS_2$ [M + H]$^+$: 231.0877; found: 231.0876.

3-[(2-Benzoyl)-1,3-dithiolanyl]-*N*-methoxy-*N*-methyl-propionamide (20)

Yield 70%; R_f = 0.45 (hexane–EtOAc, 9:1), colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58–2.67 (m, 4 H), 3.11 (s, 3 H), 3.58 (s, 3 H), 3.46–3.56 (m, 4 H), 7.25–7.38 (m, 3 H), 7.88–8.05 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.5, 32.1, 35.8, 39.5, 60.9, 75.8, 127.9, 129.2, 131.9, 135.6, 172.8, 196.2. IR ($CHCl_3$): 2816, 1689, 1676, 1492, 1347 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3S_2$: C, 55.36, H, 5.88, N, 4.30, S, 19.71. Found: C, 55.49; H, 5.63; N, 4.31; S, 19.10.

2-[Butoxy(phenyl)methylene]-1,3-dithiolane (26)

Yield 68%; R_f = 0.6 (hexane–EtOAc, 9.5:0.5), colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 7.2 Hz), 1.36–1.42 (m, 2 H), 1.57–1.60 (m, 2 H), 3.27–3.29 (m, 4 H), 3.58 (t, 2 H, *J* = 6.4 Hz), 7.17–7.19 (m, 1 H), 7.27–7.30 (m, 1 H), 7.39–7.41 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 19.3, 32.0, 36.4, 38.9, 70.4, 123.9, 127.3, 128.1, 135.2, 141.9. IR ($CHCl_3$): 2927, 1541, 1489, 1457, 1276, 1094 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{14}H_{18}OS_2$ [M + H]$^+$: 267.0877; found: 267.0878.

Ethyl 2-[1-(1,3-Dithiolan-2-ylidene)oct-2-ynyloxy]acetate (27)

Yield 65%; R_f = 0.3 (hexane–EtOAc, 8.5:1.5), yellow colored syrup. ^{1}H NMR (400 MHz, $CDCl_3$): d = 0.84 (t, 3 H, *J* = 7.2 Hz), 1.25–1.31 (m, 7 H), 1.33–1.40 (m, 2 H), 2.34 (t, 2 H, *J* = 7.2 Hz), 3.29–3.33 (m, 4 H), 4.18 (q, 2 H, *J* = 7.2 Hz), 4.62 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.1, 19.6, 22.1, 28.1, 30.9, 37.7, 38.6, 60.9, 66.2, 73.1, 101.2, 125.1, 128.1, 169.3. IR ($CHCl_3$): 2924, 1719, 1586, 1187 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{15}H_{23}O_3S_2$ [M + H]$^+$: 315.1089; found: 315.1098.

6-(2-Methyl-1,3-dithiolan-2-yl)-2,3,4,5-tetrahydropyridine (32)

Yield 80%; R_f = 0.3 (hexane–EtOAc, 8:2), yellow solid, mp 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): d = 1.56–1.59 (m, 2 H), 1.67–1.71 (m, 2 H), 1.92 (s, 3 H), 2.50–2.55 (m, 2 H), 3.37–3.39 (m, 4 H), 3.64–3.67 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 21.7, 25.6, 31.2, 40.6, 49.6, 71.2, 170.7. IR ($CHCl_3$): 2922, 1645, 1472, 1304 cm^{-1}. HRMS (EI): *m/z* calcd for $C_9H_{16}NS_2$ [M + H]$^+$: 202.0724; found: 202.0728.

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