Heteroaromatic Decarboxylative Claisen Rearrangement Reactions

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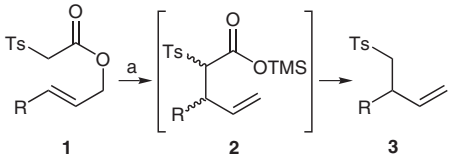
Dedicated with respect, admiration and affection to Professor Steven V. Ley, CBE, FRS, on the occasion of his 60th birthday

Abstract: Furan-2-ylmethyl, thien-2-ylmethyl and pyrrol-2-ylmethyl tosylacetates undergo facile decarboxylative Claisen rearrangement upon exposure to *N*,*O*-bis(trimethylsilyl)acetamide–potassium acetate to yield the corresponding 2,3-disubstituted heteroaromatic products in good yield. However, for 1-(thien-2-yl)ethyl tosylacetates and substrates derived from 3-(hydroxyalkyl)indoles rearomatisation does not occur.

Key words: heterocycles, heterogenous catalysis, pericyclic reactions, sulfones, tautomerism

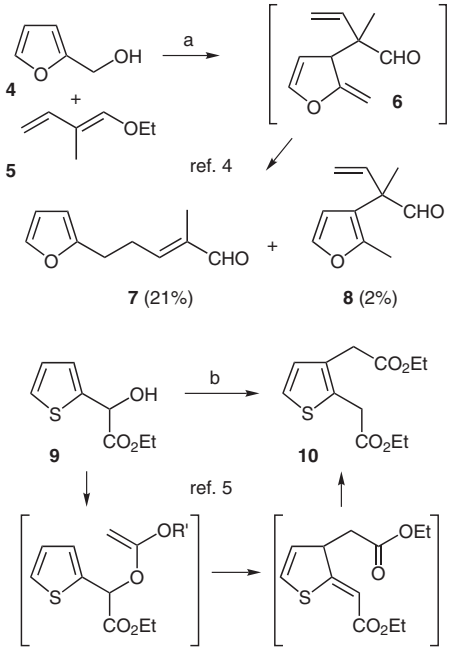
Since its discovery in 1912, the Claisen rearrangement[1] has found extensive use in synthetic organic chemistry due to the highly stereoselective nature of the [3,3]-sigmatropic process. Modern variants of this rearrangement[2] have ensured the continued use of this powerful C–C bond forming tool in organic synthesis.

Previous studies from this laboratory have demonstrated that tosylacetic esters **1** undergo Claisen rearrangement with concomitant decarboxylation when treated with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and sub-stoichiometric amounts of potassium acetate. These reactions provide sulfones **3** in excellent yields for a range of structurally diverse substrates (Scheme 1).[3] The use of microwave irradiation was found to greatly reduce the reaction time and allow the reactions to be run in the absence of solvent, without significant erosion of yield.



Scheme 1 *Reagents and conditions*: a) BSA, KOAc, PhMe, 110 °C, 15 h, 75–98% or BSA, KOAc, PhMe or no solvent, 150 °C, microwave, 3 min, 67–92%.

We became interested in applying this chemistry to substrates derived from benzylic-type alcohols, in which the rearrangement process would result in disruption of the aromatic nucleus. This idea is not without precedent. For example, when treated with diene **5**, furfuryl alcohol **4** has been reported to undergo Claisen rearrangement to give aldehydes **7** and **8**, presumably via transient intermediate **6**.[4] In addition, ethyl 2-thiopheneglycolate **9** underwent orthoester Claisen rearrangement to give 2,3-disubstituted thiophene **10** (Scheme 2).[5]



Scheme 2 *Reagents and conditions*: a) $Hg(OAc)_2$, NaOAc, 100 °C, 18 h; b) $MeC(OEt)_3$, $Me(CH_2)_4CO_2H$, reflux, 12 h then 185 °C, 6 h, 61%.

We wished to investigate whether our mild decarboxylative Claisen rearrangement (dCr) reaction conditions would bring about a similar rearrangement in heteroaromatic substrates. Esters **11**, **13** and **17** were synthesised by esterification of the corresponding (hydroxymethyl)arene with tosylacetic acid using DCC and sub-stoichiometric amounts of DMAP.[6] Alkylation of **13** with sodium hydride and allyl bromide yielded ester **15** in good yield (72%). Under the previously established dCr reaction conditions, good yields of the corresponding rearranged, decarboxylated sulfones were isolated (Table 1). The transformation of the more highly branched substrate **15**

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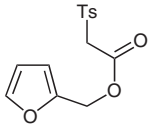
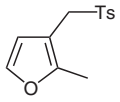
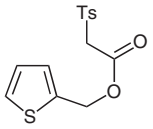
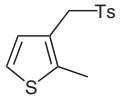
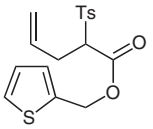
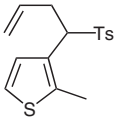
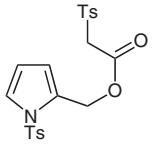
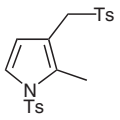
was reproducibly less efficient than those of the other substrates. Application of microwave irradiation resulted in comparable yields of rearranged products **12**, **14** and **18**, but not **16**. Microwave heating in the absence of solvent caused complete decomposition in the case of the furan and thiophene substrates. However, a good yield of **18** (70%) was obtained from the pyrrolic substrate **17** under the solvent-free conditions. The use of sub-stoichiometric amounts of BSA in the rearrangement of esters **13** and **17** gave lower yields (47% and 48%, respectively) of the corresponding sulfones.

Table 1 dCr of Heteroaromatic Tosylacetates[a]

Entry	Substrate	Product	Yield (%)[b]	
			A	B
1	 **11**	 **12**	63	75
2	 **13**	 **14**	75	22
3	 **15**	 **16**	58	–
4	 **17**	 **18**	67	77

[a] All reactions were carried out with BSA (1.0 equiv) and KOAc (0.1 equiv).
[b] Reaction conditions: A: toluene, 110 °C, 15 h; B: toluene, microwave, 150 °C, 3 min.

We next investigated heteroaromatic substrates substituted at the 3-position. Esters **19**, **20** and **21** (Figure 1) were synthesised from the corresponding alcohols in excellent yield using the DCC–DMAP procedure described previously.

In stark contrast to substrates **11**, **13**, **15** and **17**, when **19**–**21** were subjected to the stoichiometric dCr conditions no Claisen rearrangement occurred. In the case of the furan derivatives **19** and **21** only starting material was observed with a trace of decomposition product even after prolonged (30 h) reaction periods. With the thiophene derivative **20**, extensive substrate decomposition occurred. We interpret these differences in reactivity in terms of the greater electron density located at the 2-position relative to the 3-position, which results also in an attenuation of

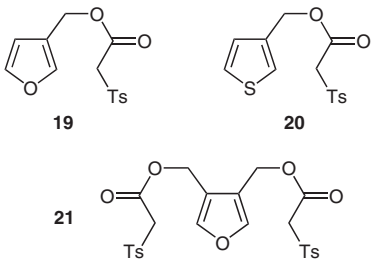
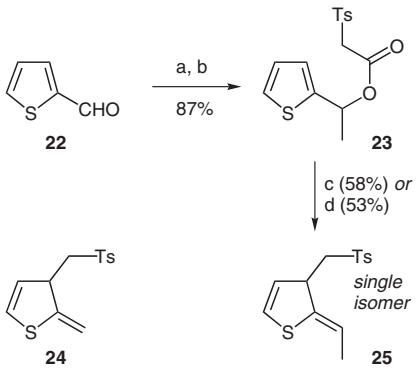


Figure 1

the weakening effect of the arene on the benzylic C–O bond in the 3-substituted versus the 2-substituted isomers.

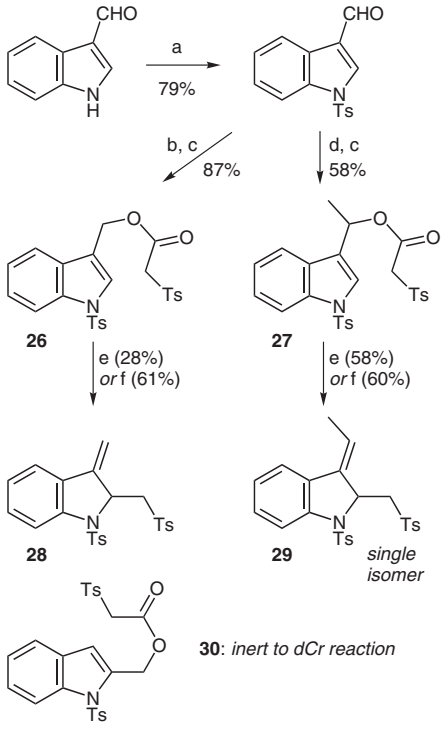
Next, we were interested in assessing the scope of the dCr reaction with respect to the extent of substitution in the 2-substituted substrates. The thiophene-containing ester **23** was readily synthesised in two steps from thiophene-2-carboxaldehyde **22**. To our surprise, exposure of ester **23** to the stoichiometric dCr resulted in the rearranged, non-aromatic product **25** as a single geometric isomer in 58% yield. Although we have not yet assigned unequivocally double bond geometry, in the isomer shown, allylic 1,3-strain appears to be minimised. Under the sub-stoichiometric conditions employed previously **25** was again obtained (53%). These observations prompted a re-examination of the dCr reaction of the more simple thiophene-containing substrate **13**, which revealed that traces of the non-aromatic product **24** had indeed been formed together with the major product sulfone **14** (Scheme 3). We speculate that the increased extent of formation of non-aromatic product in the dCr reaction of the more highly substituted substrate **23** is a consequence of (i) the more highly substituted nature of the exocyclic alkene linkage in **25** and (ii) the increase in steric buttressing which would ensue in the non-observed 2-ethyl-substituted aromatic product.

The final part of this study was devoted to extending the range of substrates to include indoles. According to the reactivity differences observed for the monocyclic heteroarene-containing substrates, we anticipated that tosylacetate substrates derived from 3-(hydroxyalkyl)in-



Scheme 3 *Reagents and conditions*: a) MeMgCl, THF, 0 °C, 2 h; b) $TsCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 15 h; c) BSA (1.0 equiv), KOAc (0.1 equiv), PhMe, 110 °C, 18 h); d) BSA (0.1 equiv), KOAc (0.1 equiv), PhMe, 110 °C, 18 h.

doles, but not the 2-substituted isomers, would be effective in this chemistry because of the greater electron density at the indole 3-position. This supposition was borne out in practice: while tosylacetate **30** was inert to the dCr conditions, substrate **26** synthesised from indole-3-carbaldehyde as depicted in Scheme 4 underwent moderately efficient rearrangement–decarboxylation using the sub-stoichiometric conditions to give the methylene-substituted indoline **28**. Furthermore, the homologous substrate **27** reacted similarly under both stoichiometric and sub-stoichiometric conditions to give **29** as a single isomer; again it has not been possible thus far to assign exocyclic alkene geometry. Methyleneindolines similar to **28** have been synthesised by Larock via palladium-catalysed heteroannulation of allenes using substituted aryl halides.[7,8] All attempts to convert indoline **28** into the isomeric indole under both acidic and basic conditions failed; the stability of **28** was demonstrated by the high-yield recovery of it in these fruitless efforts.



Scheme 4 *Reagents and conditions*: a) NaH, TsCl, THF, 0 °C→r.t., 2 h; b) $LiAlH_4$, THF, r.t., 1.5 h; c) $TsCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 15 h; d) MeMgCl, THF, 0 °C, 2 h; e) BSA (1.0 equiv), KOAc (0.1 equiv), PhMe, 110 °C, 18 h; f) BSA (0.1 equiv), KOAc (0.1 equiv), PhMe, 110 °C, 18 h.

In summary, we have demonstrated that a range of heterocyclic substrates undergo dCr to yield 2,3-disubstituted heteroarenes products in good yield. We have shown also that through careful choice of protecting group and substitution pattern, the dCr of heterocyclic substrates may be used in the synthesis of non-aromatic products. It is hoped that these readily accessible compounds will prove to be valuable building blocks in target-orientated natural product synthesis.

Conventional Heating; Typical Procedure

To a solution of ester **11** (200 mg, 0.68 mmol, 1 equiv) in toluene (6 mL) was added BSA (152 μL, 0.75 mmol, 1.1 equiv) and KOAc (6.7 mg, 0.07 mmol, 0.1 equiv); the mixture was heated at 110 °C for 15 h. Concentration under reduced pressure and chromatography (EtOAc–petroleum ether, 1:4) gave furan **12** (108 mg, 63%) as colourless crystals.

Microwave Heating; Typical Procedure

To a microwave vial was added KOAc (3.3 mg, 0.03 mmol, 0.1 equiv) followed by ester **11** (100 mg, 0.34 mmol, 1 equiv), BSA (91.7 μL, 0.37 mmol, 1.1 equiv) and toluene (1 mL). The resulting mixture was heated to 150 °C (250 W) for 3 min. Concentration under reduced pressure and chromatography (EtOAc–petroleum ether, 1:4) gave furan **12** (63.4 mg, 75%) as colourless crystals.

12

R_f 0.33 (EtOAc–petroleum ether, 1:4); colourless crystals; mp 72–74 °C.

IR (film): 2924, 1597, 1517, 1446, 1403, 1316, 1303, 1290, 1231, 1188, 1144, 1086, 899, 816, 765, 733, 665, 640 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.54 (2 H, d, *J* = 8.0 Hz, *o*-Ph), 7.24 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 7.17 (1 H, d, *J* = 2.0 Hz, H-5), 6.14 (1 H, d, *J* = 2.0 Hz, H-4), 4.04 (s, 2 H, CH_2), 2.39 (s, 3 H, CH_3Ph), 1.82 (s, 3 H, CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 152.3, 144.8, 140.7, 135.0, 129.7, 128.6, 112.2, 107.4, 53.8, 21.7, 11.1.

MS (CI): *m*/*z* = 268 $[M + NH_4]^+$, 205, 188, 155, 107, 98, 81.

HRMS: *m*/*z* calcd for $C_{13}H_{18}NSO_3$ $[M + NH_4]^+$, 268.1001; found, 268.1011.

Anal. Calcd for $C_{13}H_{14}O_3S$: C, 62.18; H, 5.45. Found: C, 62.38; H, 5.64.

14

R_f 0.21 (EtOAc–petroleum ether, 1:4); colourless crystals; mp 134–136 °C.

IR (film): 3055, 2985, 1598, 1442, 1421, 1315, 1265, 1147, 1086, 895, 731 704, 634, 609 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.49 (2 H, d, *J* = 8.0 Hz, *o*-Ph), 7.24 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 6.98 (1 H, d, *J* = 5.0 Hz, H-5), 6.75 (1 H, d, *J* = 5.0 Hz, H-4), 4.24 (2 H, s, CH_2), 2.41 (3 H, s, CH_3Ph), 2.00 (3 H, s, CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 144.8, 135.4, 129.7, 129.6, 129.5, 128.6, 121.9, 112.4, 55.9, 21.7, 12.7.

MS (CI): *m*/*z* = 284 $[M + NH_4]^+$, 128, 111.

HRMS: *m*/*z* calcd for $C_{13}H_{18}NO_2S_2$ $[M + NH_4]^+$, 284.0779; found, 284.0789.

16

R_f 0.28 (EtOAc–petroleum ether, 1:4); pale yellow oil.

IR (film): 3080, 2922, 1641, 1597, 1441, 1311, 1290, 1209, 1146, 1086, 993, 920, 815, 705, 661 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.78 (1 H, d, *J* = 8.0 Hz, *o*-Ph), 7.38 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 7.17 (1 H, d, *J* = 8.0 Hz, *o*-Ph), 7.00 (2 H, s, H-4, H-5), 5.57–5.42 (1 H, m, C*H*=CH_2), 5.09–4.92 (2 H, m, CH=CH_2), 4.13 (1 H, dd, *J* = 11.5, 4.0 Hz, $CHOSO_2$), 3.21–3.09 (1 H, m, CH*H*CH=CH_2), 2.87–2.73 (1 H, m, C*H*HCH=CH_2), 2.38 (3 H, s, CH_3Ph), 1.81 (3 H, s, CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 144.7, 133.1, 130.3, 130.1, 129.4, 129.0, 127.2, 122.0, 118.4, 106.5, 64.3, 32.0, 21.7, 12.5.

MS (CI): *m*/*z* = 324 $[M + NH_4]^+$, 307 $[M + H]^+$, 301, 247, 205, 177, 167, 151.

HRMS: *m*/*z* calcd for $C_{16}H_{22}NO_2S_2$ $[M + NH_4]^+$, 324.1092; found, 324.1093.

18

R_f 0.14 (EtOAc–petroleum ether, 3:7); colourless crystals; mp 170–172 °C.

IR (film): 3055, 2987, 2925, 1597, 1421, 1367, 1315, 1267, 1173, 1161, 1146, 1088, 1028, 897, 814, 750, 704, 688, 646 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.62 (2 H, d, *J* = 8.5 Hz, *o*-Ph), 7.35 (2 H, d, *J* = 8.0 Hz, *o*-Ph), 7.31 (2 H, d, *J* = 8.5 Hz, *m*-Ph), 7.23 (1 H, d, *J* = 3.5 Hz, H-5), 7.02 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 6.10 (1 H, d, *J* = 3.5 Hz, H-4), 4.00 (2 H, s, CH_2), 2.44 (3 H, s, $CH_2OSO_2PhCH_3$), 2.34 (3 H, s, $NOSO_2PhCH_3$), 1.73 (3 H, s, CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 145.2, 144.6, 134.6, 130.4, 130.1, 129.5, 128.6, 127.2, 126.9, 121.5, 113.3, 54.6, 21.8, 21.7, 10.3.

MS (CI): *m*/*z* = 421 $[M + NH_4]^+$, 404 $[M + H]^+$, 362, 267, 250, 189, 94.

HRMS: *m*/*z* calcd for $C_{20}H_{25}N_2O_4S_2$ $[M + NH_4]^+$, 421.1256; found, 421.1257.

Anal. Calcd for $C_{20}H_{21}NO_4S_2$: C, 59.48; H, 5.36; N, 3.54. Found: C, 59.53; H, 5.25; N, 3.47.

25

R_f 0.42 (EtOAc–petroleum ether, 2:3); colourless oil.

IR (film): 3063, 2969, 2924, 1596, 1449, 1404, 1316, 1301, 1289, 1149, 1086, 1018, 848, 815, 766, 707, 696 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.78 (2 H, d, *J* = 8.5 Hz, *o*-Ph), 7.34 (2 H, d, *J* = 8.5 Hz, *m*-Ph), 6.23 (1 H, dt, *J* = 6.5, 1.5 Hz, H-5), 5.82 (1 H, dd, *J* = 6.5, 2.5 Hz, H-4), 5.48 (1 H, qdd, *J* = 6.5, 2.0, 1.0 Hz, C=C*H*CH_3), 4.12–4.03 (1 H, m, H-3), 3.26 (1 H, dd, *J* = 14.0, 10.0 Hz, C*H*HTs), 3.14 (1 H, dd, *J* = 14.0, 3.5 Hz, CH*H*Ts), 2.42 (3 H, s, CH_3Ph), 1.60 (3 H, dd, *J* = 6.5, 2.0 Hz, C=CHCH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 145.1, 140.9, 136.6, 130.1, 128.0, 124.8, 124.3, 117.4, 63.4, 46.8, 21.8, 17.0.

MS (CI): *m*/*z* = 298 $[M + NH_4]^+$, 150, 124, 61.

HRMS: *m*/*z* calcd for $C_{14}H_{20}NO_2S_2$ $[M + NH_4]$, 298.0935; found, 298.0930.

28

R_f 0.33 (EtOAc–petroleum ether, 2:3); colourless oil.

IR (film): 3062, 2957, 2925, 1598, 1493, 1461, 1359, 1318, 1267, 1170, 1140, 1088, 1045, 1020, 971, 814, 753, 737, 659 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.83 (2 H, d, *J* = 8.0 Hz, *o*-Ph), 7.67 (1 H, d, *J* = 8.0 Hz, H-4), 7.47 (2 H, d, *J* = 8.0 Hz, *o*-Ph), 7.37 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 7.34–7.01 (3 H, m, H-5, H-6, H-7), 7.14 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 5.59–5.49 (2 H, m, $C=CH_2$), 4.98 (1 H, dd, *J* = 8.0, 2.0 Hz, C*H*HTs), 4.01 (1 H, dd, *J* = 14.5, 2.0 Hz, CH*H*Ts), 3.67 (1 H, dd, *J* = 14.5, 8.0 Hz, H-2), 2.46 (3 H, s, $CH_2OSO_2PhCH_3$), 2.32 (3 H, s, $NOSO_2PhCH_3$).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 145.0, 144.7, 142.8, 137.4, 133.0, 130.2, 130.0, 129.9, 129.2, 128.3, 127.5, 125.0, 121.1, 116.5, 106.9, 62.7, 60.3, 21.8, 21.7.

MS (CI): *m*/*z* = 471 $[M + NH_4]^+$, 317, 302, 300, 188, 174, 144, 132, 108.

HRMS: *m*/*z* calcd for $C_{24}H_{27}N_2O_4S_2$ $[M + NH_4]^+$, 471.1412; found, 471.1412.

29

R_f 0.31 (EtOAc–petroleum ether, 3:7); colourless oil.

IR (film): 2958, 2924, 2863, 1596, 1457, 1399, 1357, 1320, 1302, 1168, 1141, 1087, 944, 813, 750, 737, 660 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.76 (2 H, d, *J* = 8.0 Hz, *o*-Ph), 7.62 (1 H, d, *J* = 8.0 Hz, H-4), 7.45 (2 H, d, *J* = 8.0 Hz, *o*-Ph), 7.40 (1 H, d, *J* = 7.5 Hz, H-7), 7.31 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 7.22–7.01 (2 H, m, H-5, H-6), 7.11 (2 H, d, *J* = 8.0 Hz, *m*-Ph), 5.96 (1 H, qd, *J* = 7.0, 1.5 Hz, C=C*H*CH_3), 5.04–4.96 (1 H, m, H-1), 3.83 (1 H, dd, *J* = 14.5, 3.0 Hz, CH*H*Ts), 3.63 (1 H, dd, *J* = 14.5, 8.0 Hz, C*H*HTs), 2.41 (3 H, s, $CH_2OSO_2PhCH_3$), 2.28 (3 H, s, $NOSO_2PhCH_3$), 1.84 (3 H, dd, *J* = 7.5, 1.5 Hz, C=CHCH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 144.8, 144.5, 143.3, 137.6, 134.3, 133.6, 129.9, 129.8, 128.9, 128.1, 127.4, 125.1, 124.9, 122.3, 116, 62.7, 61.4, 21.8, 21.6, 14.3.

MS (CI): *m*/*z* = 485 $[M + NH_4]^+$, 391, 337, 314, 256, 236, 220, 188, 77.

HRMS: *m*/*z* calcd for $C_{25}H_{29}N_2S_2O_4$ $[M + NH_4]^+$, 485.1569; found, 485.1553.

Acknowledgment

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