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Copper-Catalyzed Three-Component Synthesis of 2-Iminodihydrocoumarins and 2-Iminocoumarins

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Abstract: An efficient synthesis of *N*-sulfonyl-substituted 2-imino-3,4-dihydrocoumarins and 2-iminocoumarins *via* a copper-catalyzed multicomponent reaction of sulfonyl azides with terminal alkynes and β-(*ortho*-hydroxyphenyl)-α,β-unsaturated ketones or *ortho*-hydroxyphenylpropiolates has been developed. The cascade process involves trapping the keteimine by a nucleophilic addition and an intramolecular Michael addition. This methodology could well be extended to the concise synthesis of the polysubstituted piperidine scaffold.

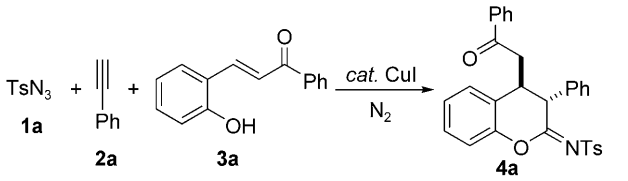
Keywords: cascade reactions; copper; coumarins; ketenimines; multicomponent reactions

Iminocoumarins are one type of protein tyrosine kinase (PTK) inhibitors that are most valuable for the treatment of diseases involving excess cell proliferation as well as the antitumor process.[1] They are also useful fluorescent dyes in fields as various as cell biology, medical analysis and sensors.[2] Classic methods for synthesis of iminocoumarins, such as Knoevenagel condensation and modification from coumarins, suffer from several shortcomings including limited substituents and troublesome chemical process management.[3] In order to overcome these shortages, here we would like to report a concise synthesis of iminocoumarins *via* multicomponent reactions that are versatile with regard to the substrate scope and the synthetic applicability.

Recently, we[4] and others[5] have developed Cu-catalyzed three-component reactions of sulfonyl azides with terminal alkynes and a number of nucleophiles, such as amines, alcohols as well as water. These reactions involve a copper-catalyzed azide-alkyne cycloaddition (CuAAC) and the generation of ketenimine intermediate by nucleophiles. Instead of sulfonyl azides, phosphoryl azides could also participate in the reaction and afford three component adducts.[6] As an extension of our previous work, here we use β-(*ortho*-hydroxyphenyl)-α,β-unsaturated ketones as substrates, with both nucleophilicity and electrophilicity, for trapping the ketenimine intermediates. Fortunately, 2-iminocoumarins were ideally obtained in moderate yields and with *trans* as the predominant configuration.

The CuI-catalyzed reaction of toluenesulfonyl azide (**1a**) with phenylacetylene (**2a**) and chalcone (**3a**) was used to screen the reaction conditions (Table 1). Triethylamine (TEA, 1 equiv.) was proven to be the

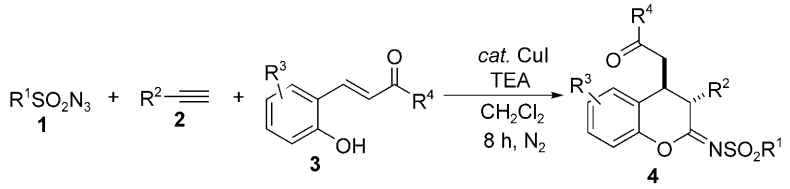
Table 1. Optimization of reaction conditions for the synthesis of iminodihydrocoumarin **4a**.[a]



Entry	Base	Solvent	Time [h]	Yield[b] [%]	*dr*[c]
1	Et_3N	CH_2Cl_2	8	86	95:5
2	Et_3N	CH_3CN	8	72	95:5
3	pyridine	CH_2Cl_2	8	83	92:8
4	pyridine	CH_3CN	12	55	90:10
5	2,6-luitidine	$CHCl_3$	8	75	95:5
6	K_2CO_3	CH_2Cl_2	12	47	90:10

[a] *Reaction conditions:* **1a** (0.6 mmol), **2a** (0.6 mmol), **3a** (0.5 mmol), CuI (0.06 mmol), the indicated base (0.6 mmol) and solvent (5 mL).
[b] Yield of the isolated product.
[c] The ratio was determined by ^{1}H NMR spectroscopy of the crude product.

Table 2. Three-component reaction of azides **1** with alkynes **2** and chalcones **3**.[a]



Entry	**1** (R^1)	**2** (R^2)	**3** (R^3/R^4)	Product **4**/Yield [%][b]
1	**1a** (4-MeC_6H_4)	**2a** (Ph)	**3a** (H/Ph)	**4a**/86[c]
2	**1b** (Ph)	**2b** (4-$MeOC_6H_4$)	**3a**	**4b**/73[c]
3	**1c** (4-ClC_6H_4)	**2c** (4-MeC_6H_4)	**3a**	**4c**/81[c]
4	**1d** (5-Me_2N-naphth-1-yl)	**2d** (4-FC_6H_4)	**3a**	**4d**/75[c]
5	**1a**	**2e** (*n*-Bu)	**3a**	**4e**/97[d]
6	**1a**	**2f** (1-cyclohexenyl)	**3a**	**4f**/88[c]
7	**1e** (Me)	**2a**	**3b** (H/4-ClC_6H_4)	**4g**/83[c]
8	**1b**	**2f**	**3b**	**4h**/85[c]
9	**1c**	**2a**	**3c** (H/2-MeC_6H_4)	**4i**/71[c]
10	**1b**	**2c**	**3c**	**4j**/79[c]
11	**1a**	**2b**	**3d** (4-Br/Ph)	**4k**/69[c]
12	**1c**	**2e**	**3d**	**4l**/74[e]
13	**1a**	**2g** (4-EtC_6H_4)	**3d**	**4m**/81[c]
14	**1a**	**2a**	**3e** (3-MeO/Ph)	**4n**/80[c]
15	**1a**	**2f**	**3e**	**4o**/85[c]
16	**1a**	**2a**	**3f** (H/Me)	**4p**/46[c]

[a] *Reaction conditions:* **1** (0.6 mmol), **2** (0.6 mmol), **3** (0.5 mmol), CuI (0.06 mmol), TEA (0.6 mmol), CH_2Cl_2 (5 mL), room temperature, 8 h.
[b] Isolated yield.
[c] $dr > 95:5$ based on ^{1}H NMR spectroscopy of the crude product.
[d] $dr \approx 88:12$.
[e] $dr \approx 82:18$.

most effective base among those others tested, such as pyridine, 2,6-lutidine and potassium carbonate (Table 1, entries 1, 3–6). As to the solvent, in comparison with acetonitrile, dichloromethane not only provided a higher isolated yield but also a higher diastereomeric ratio ($dr = 95:5$) in favour of the *trans* isomer (Table 1, entries 1 and 2).

With the optimized reaction conditions in hand, we tested the substrate diversity with a variety of azides, alkynes and chalcones (Table 2). In all cases, the reactions afforded the corresponding *N*-toluenesulfonyliminodihydrocoumarins **4a**–**4p** in 46–97% yields. The stereoselectivity of the reaction was related to the character of alkynes. Arylacetylenes **2a**–**2d** and **2g** (Table 2, entries 1–4, 7, 9–11, 13, 14, and 16) and cyclohexenylacetylene (**2f**) (Table 2, entries 6, 8, and 15) underwent this cascade reaction smoothly with excellent diastereomeric ratios ($dr > 95:5$) while 1-hexyne (**2e**) gave a slightly decreased diastereomeric ratio (Table 2, entries 5 and 12).

The structures of the products was fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy as well as high-resolution mass spectrometry (see Supporting Information). The structure of **4h** was further established by a single crystal X-ray analysis (Figure 1),[7] which clearly presented the *trans* configuration.

Based on our previous works, a possible mechanism was proposed and is shown in Scheme 1. Firstly, ketenimine **A** could be formed by the Cu-catalyzed cycloaddition reaction of azides **1a** and alkynes **2a** *via* a click reaction and a subsequent release of N_2.[4,5] Then nucleophile **B**, deprotonated by triethylamine, could then attack the central carbon of **A** to form **C**.

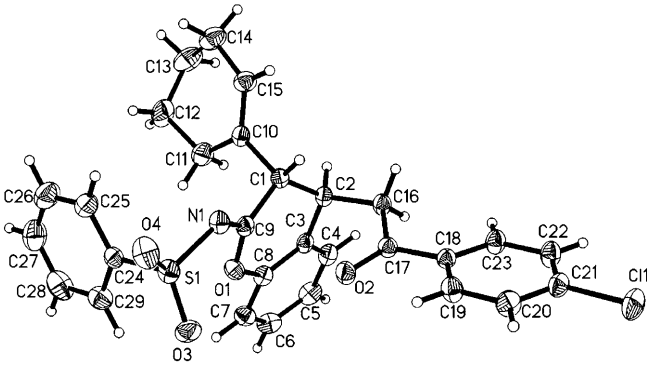
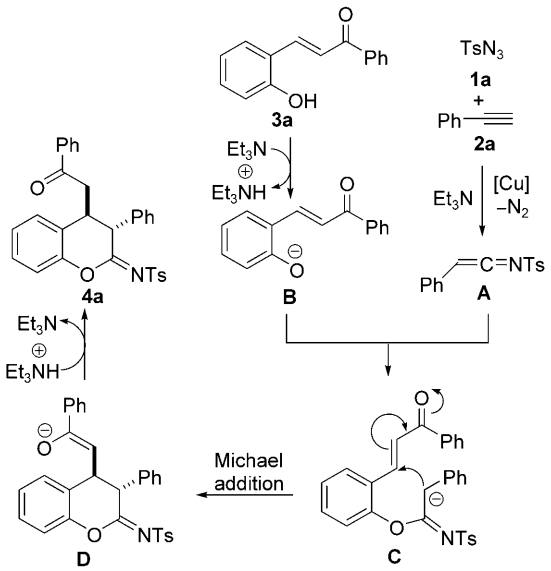
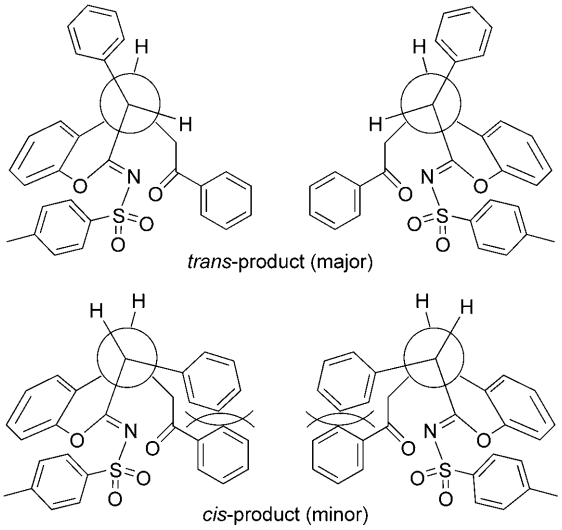


Figure 1. X-ray crystal structure of **4h**.



Scheme 1. Possible mechanism for the formation of **4a**.

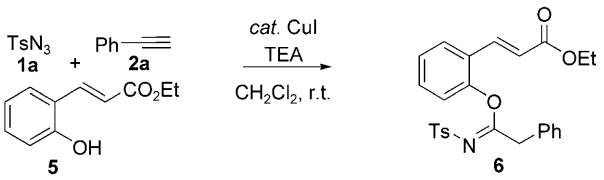


Scheme 2. Depiction of the *trans* stereocontrol of **4a**.

Finally, **C** could undergo an intramolecular Michael addition and a sequential proton transfer to afford the iminodihydrocoumarin **4a**.

As shown in Figure 1, the iminodihydrocoumarin ring exists in a twisted planar form. The vicinal coupling constant (^3J) for two protons on C-1 and C-2 is not clearly shown in the ^{1}H NMR spectrum because the dihedral angle of H–C-1–C-2–H is 92.77°. Based on the Karplus relation, ^3J is calculated to be 2.07 Hz. Meanwhile, the structures of both *trans*-**4h** and *cis*-**4h** have been optimized by the RHF/6-31G(d) method. The dihedral angles of H–C-1–C-2–H in *trans*-**4h** and *cis*-**4h** are calculated to be 96° and 48°, respectively. Hence, the ^3J values are calculated to be 2.21 Hz for *trans*-**4h** and 8.2 Hz for *cis*-**4h**. Based on these calculated results and ^{1}H NMR data, we assigned all compounds **4** as having the *trans* configuration. The observed diastereoselectivity could be rationalized by two factors. One is the steric hindrance (Scheme 2) and the second is the result of the thermodynamic equilibration. By calculation of the energy potentials of *trans*-**4h** and *cis*-**4h** [RHF/6-31G(d) method], *trans*-**4h** is more stable than *cis*-**4h** and the energy difference is 3.41 kcal·mol^{-1}. In comparison to aromatic acetylenes (**2a**–**2d)** and cyclohexenylacetylene (**2g**), 1-hexyne (**2f**) gave a relatively lower diastereoselectivity due to the fact that the steric hindrance has been released a little when the *cis* configuration is adopted in the step of the Micheal addition.

In order to extend the substrate diversity, *ortho*-hydroxyphenyl-α,β-unsaturated ester **5** was tested for this cascade reaction. Unfortunately, although trapping the ketenimine by phenolic anion was observed in this case, we did not detect the sequential intramolecular Michael addition product. The three-component adduct product **6** was obtained in 90% isolated yield (Scheme 3).

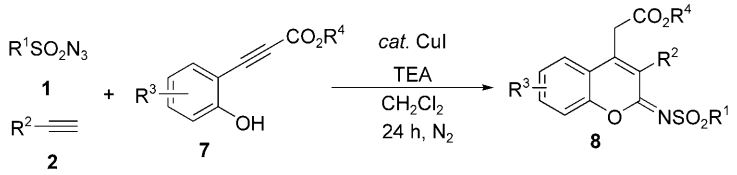


Scheme 3. Three-component reaction of **1a**, **2a** and **5**.

Rather than altering the ketone to an ester, we tried to change C=C into C≡C. However, many attempts at synthesis of 3-(2-hydroxyphenyl)-1-phenylprop-2-yn-1-one failed because this expected compound was too unstable and would intramolecularly cyclize to benzofuran-2-yl(phenyl)methanone in high yield.

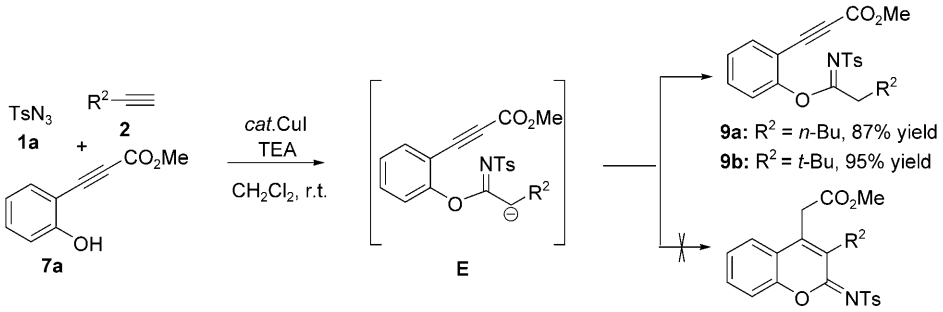
Based on the above survey, we used *ortho*-hydroxyphenylpropiolates **7**, which couple an ester group and a C≡C bond, to test the reality of this cascade reaction. Fortunately, the anticipated iminocoumarins **8** were obtained in high yields (Table 3). Both aromatic sulfonyl azides (Table 3, entries 1–8 and 10–17) and aliphatic sulfonyl azide (Table 3, entry 9) gave iminocoumarins in good to excellent yields. An electronic effect, either by a conjugative effect or by an inductive effect, on the aromatic sulfonyl azides **1**, aromatic acetylenes **2** and phenylpropiolates **7** did not affect the reaction. Hex-1-yne (**2e**) and 3,3-dimethylbut-1-yne (**2j**) afforded **9a** and **9b** in 87% and 95% yields, respectively (Scheme 4). In these cases, the basicity of intermediate **E** was increased. Therefore it preferred abstraction of a proton instead of a sequential Michael addition.

Table 3. Three-component reaction of azides **1** with alkynes **2** and phenylpropiolates **7**.[a]



Entry	**1** (R^1)	**2** (R^2)	**7** (R^3/R^4)	Product **8**/Yield[b] [%]
1	**1a** (4-MeC_6H_4)	**2a** (Ph)	**7a** (H/Me)	**8a/**92
2	**1b** (Ph)	**2a**	**7a**	**8b/**91
3	**1a**	**2b** (4-$MeOC_6H_4$)	**7a**	**8c/**90
4	**1a**	**2c** (4-MeC_6H_4)	**7a**	**8d/**96
5	**1a**	**2g** (4-EtC_6H_4)	**7a**	**8e/**98
6	**1a**	**2a**	**7a**	**8f/**95
7	**1f** (4-$O_2NC_6H_4$)	**2a**	**7a**	**8g/**92
8	**1g** (4-$AcNHC_6H_4$)	**2a**	**7a**	**8h/**93
9	**1e** (Me)	**2a**	**7a**	**8i/**87
10	**1c** (4-ClC_6H_4)	**2c**	**7a**	**8j/**92
11	**1f**	**2b**	**7a**	**8k/**81
12	**1a**	**2h** (4-*t*-BuC_6H_4)	**7a**	**8l/**96
13	**1a**	**2i** (3-ClC_6H_4)	**7a**	**8m/**90
14	**1a**	**2a**	**7b** (H/Et)	**8n/**94
15	**1a**	**2a**	**7c** (H/Bn)	**8o/**93
16	**1a**	**2a**	**7d** (4-Cl/Me)	**8p/**91
17	**1a**	**2a**	**7e** (4-Me/Me)	**8q/**93

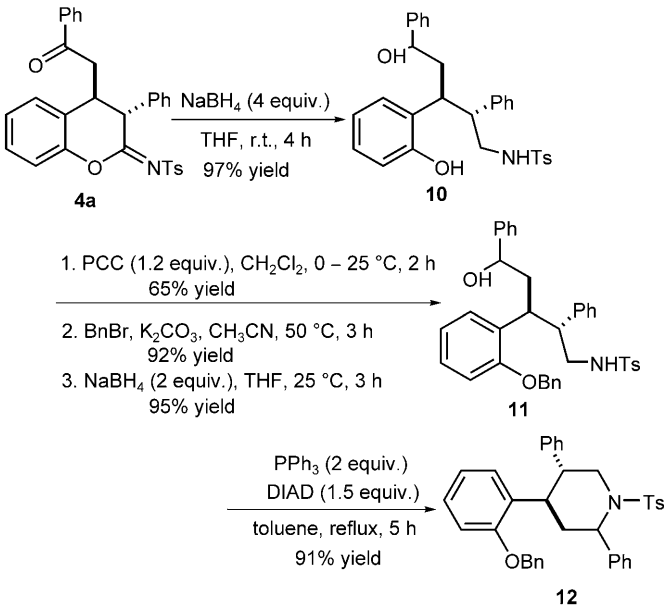
[a] *Reaction conditions:* **1** (1.2 mmol), **2** (1.2 mmol), **7** (1.0 mmol), CuI (0.1 mmol), CH_2Cl_2 (10 mL) , TEA (1.2 mmol), room temperature, 24 h.
[b] Isolated yield.



Scheme 4. Three-component reaction of propiolate **7a** with azide **1a** and alkynes **2**.

To highlight the utility of this methodology, typically with high diasteroselectivity in the case of (*ortho*-hydroxyphenyl)-α,β-unsaturated ketones, we synthesized **4a** on a gram scale and converted it into synthetically and biologically useful molecules such as the substituted piperidine **12** (Scheme 5).[8] In this procedure, **4a** was firstly reduced by $NaBH_4$ to afford **10**. Oxidation of secondary alcohol **10** to the ketone, followed by protection of the phenolic OH and then reduction by $NaBH_4$ furnished **11** smoothly. Finally, *via* an intramolecular Mitsunobu reaction, **12** was obtained. Selective protection of the phenolic OH of **10** failed. As a net result, starting from chalcone (**3a**), piperidine **12** could be prepared in six steps and with a total yield of 43%.

In conclusion, we have developed an efficient and highly diastereoselective synthesis of *N*-sulfonyl-substituted 2-iminodihydrocoumarins and 2-iminocoumarins *via* a copper-catalyzed three-component reaction of sulfonyl azides with terminal alkynes and β-(*ortho*-hydroxyphenyl)-α,β-unsaturated ketones or *ortho*-hydroxyphenylpropiolates. The *trans*-iminodihydrocoumarins could be applied for the stereoselective synthesis of chiral piperidine scaffolds. Investigations on more synthetic applications of the present approach are underway in our laboratory.



Scheme 5. Synthesis of piperidine **12** from **4a**.

Experimental Section

General Procedure for the Synthesis of Iminodihydrocoumarins 4

Triethylamine (0.6 mmol) was slowly added into a solution of azide **1** (0.6 mmol), alkyne **2** (0.6 mmol), chalcone **3** (0.5 mmol) and CuI (0.06 mmol) in CH_2Cl_2 (5 mL) over 3–5 min under a nitrogen atmosphere at room temperature. After the reaction mixture had been stirred at the same temperature for 8 h, the solution was diluted with CH_2Cl_2 (20 mL). The organic phase was then washed with water (10 mL) and brine (10 mL), and dried over sodium sulfate. After fitration, the solvent was removed under vacuum and the residue was subject to flash chromatography on silica gel (petroleum ether/ethyl acetate, 3:1 to 1:2).

General Procedure for the Synthesis of Iminocoumarins 8

Triethylamine (1.2 mmol) was slowly added into a solution of azide **1** (1.2 mmol), alkyne **2** (1.2 mmol), phenylpropiolate **7** (1.0 mmol) and CuI (0.1 mmol) in CH_2Cl_2 (10 mL) over 3–5 min under a nitrogen atmosphere at room temperature. After the reaction mixture had been stirred at the same temperature for 24 h, the solution was diluted with CH_2Cl_2 (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL), and dried over sodium sulfate. After filtration, the solvent was removed under vacuum and the residue was subject to flash chromatography on silica gel (petroleum ether/ethyl acetate, 3:1 to 1:2) to afford pure **8**.

Data for compound 4a: white solid; mp 173–175 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.90$ (m, 4H), 7.59 (m, 1H), 7.46 (m, 2H), 7.31–7.15 (m, 7H), 7.07 (m, 4H), 4.19 (s, 1H), 4.03 (m, 1H), 3.34 (dd, $J = 8.0$, 18.0 Hz, 1H), 3.17 (dd, $J = 5.2$, 18.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 196.6$, 165.4, 149.9, 143.7, 138.2, 136.2, 136.1, 133.7, 129.3, 129.0, 128.8, 128.7, 128.0, 127.61, 127.57, 126.9, 126.0, 123.7, 116.6, 48.5, 43.4, 37.1, 21.6; IR (KBr): $\nu = 2950$, 1686, 1639, 1598, 1332, 1157, 769 cm^{-1}; MS (ESI): $m/z =$ 494.3 ([M−H]$^-$); HR-MS (ESI): $m/z = 518.1385$, calcd for $C_{30}H_{25}NO_4S + Na^+$ ([M+Na]$^+$): 518.1397.

Data for compound 8a: white solid; mp 205–206 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.81$ (d, $J = 8.4$ Hz, 2H), 7.60–7.55 (m, 2H), 7.50–7.48 (m, 2H), 7.44–7.39 (m, 2H), 7.39–7.35 (t, $J = 8.0$ Hz, 1H), 7.28–7.26(m, 2H), 7.23 (d, $J =$ 8.4 Hz, 2 H), 3.68 (s, 5H), 2.38(s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.4$, 158.1, 151.7, 142.8, 142.7, 139.2, 133.2, 131.9, 130.8, 129.5, 129.0, 128.6, 128.5, 126.9, 125.7, 124.8, 119.7, 117.0, 52.7, 35.8, 21.4; IR (KBr): $\nu = 1742$, 1620, 1544, 1450, 1318, 1088, 1157, 777 cm^{-1}; MS (ESI): $m/z = 470.0$ ([M+Na]$^+$); HR-MS (ESI): $m/z = 470.1022$, calcd for $C_{25}H_{21}NO_5S + Na^+$ ([M+Na]$^+$): 470.1033.

Acknowledgements

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[7] CCDC 695148 contains the supplementary crystallographic data for compound **4h**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif, or by emailing data request @ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336033.

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