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ONE-POT THREE COMPONENET REACTION FOR THE SYNTHESIS OF 2-ALKYLTHIO-3-AROYLIMIDAZO[2,1-*a*]ISOQUINOLINE IN AQUEOUS MEDIA

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Abstract - A one-pot, three component reaction between isoquinoline, phenacyl bromide derivatives and thiocyanates leading to imidazo[2,1-*a*]isoquinoline derivatives in good yields is reported. Reactions are carried out in water or DMF as the solvent at reflux.

INTRODUCTION

Synthesis of imidazo[1,2-*a*]pyridines and imidazo[2,1-*a*]isoquinolines has attracted significant attention in recent years due to their pharmacological characteristics.[1,2,3,4,5,6,7,8,9,10,11,12] For example this class of compounds exhibit anti-inflammatory,[8] potential antirhinoviral,[9] long-acting local anesthetic,[10] antiulcer,[9,11] and antihelmintic or bacteriostatic activities.[12]

However several methods reported in the literature for preparation of imidazo[1,2-*a*]pyridines based on the use of 2-aminopyridines or other suitably substituted pyridines or approaches based on the use of substituted imidazoles as starting materials,[13,14,15,16,17,18,19,20,21,22,23,24] only a few methods for the preparation of imidazo[2,1-*a*]isoquinolines have been reported and there is a definite need to develop a more structurally flexible method of the synthesis of this class of compounds.

2-Aryl substituted derivatives of imidazo[2,1-*a*]isoquinolines can be prepared by reaction of *N*-phenacylisoquinolinum bromide and hydroxylamine hydrochloride.[25] In another method imidazo[2,1-*a*]isoquinolines have been prepared by the 1,5-dipolar cyclization reaction of isoquinolinum *N*-ylids using *N*-bis(methylthio)methylenesulfoneamide derivatives which are prepared, in turn, by the condensation of *p*-toluenesulfonamide with carbon disulfide in DMSO in the presence of sodium hydroxide and treatment of the intermediate with dimethyl sulfate.[26] Also reaction of α-bromoacetophenone phenylsulfonylhydrazones with isoquinoline has been reported which leads to respective 2-arylimidazoisoquinoline formation together with releasing benzenesulfonamide.[27]

Phenylsulfonylhydrazones required for this procedure are prepared, in turn, by the reaction of α-bromoketones with phenylsulfonylhydrazine. Also 1,3-dipolar cycloaddition reaction of trifluoroacetonitrile with heterocycle ylides has been reported which leads to corresponding imidazo[2,1-*a*]isoquinolines in 4-20% yield.[28] This class of compounds also have been prepared via reaction of 3-aminocinnamonitrile and 3-aminocrotononitrile with isoquinoline *N*-oxide in the presence of benzoyl chloride.[29] However, these methods suffer from the difficulties with preparation of suitable starting materials and/or low yields of conversion.

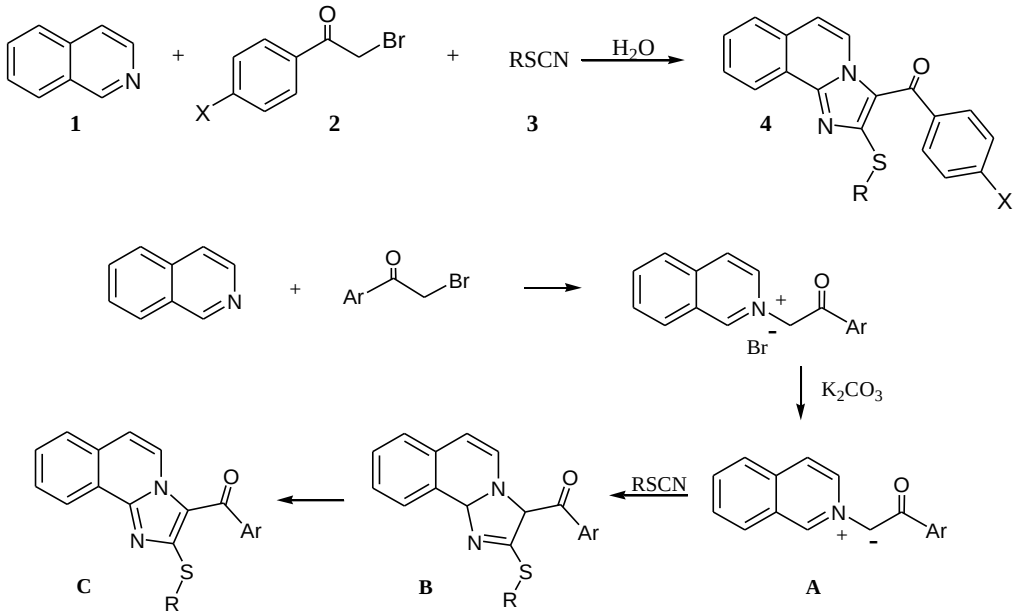
The design of multicomponent reactions (MCR) is an important field of research from the point of view of combinatorial chemistry.[30] MCRs are highly efficient,[31] not only due to their convergent nature, but also because of superior atom economy[32] and straitforward experimental procedures.

Due to the natural abundance of water as well as the inherent advantages of using water as a solvent, recently interest has been growing in studying organic reactions in water.[33]

Ylide research has been developed in recent years and ylides have now become powerful and versatile synthetic tools in organic chemistry.[34]

RESULTS AND DISCUSSION

Herein, we report an innovative and efficient synthesis of imidazo[2,1-*a*]isoquinolines via a one-pot three component reaction of isoquinolines, phenacyl bromides and thiocyanates, through formation of isoquinoline ylides in aqueous medium. (Scheme 1)



Scheme1

To explore the scope and versatility of this method, various reaction conditions were investigated, including solvent and temperature variations. Highlighted in Table 1 for compound **4b** (R=Et, X=H), for example is the influence of solvent and temperature on the reaction yield. To optimize reaction conditions

with temperature, the same reaction was carried out, in each solvent, at room temperature and reflux conditions.

It is shown in Table 1 that the reaction using H_2O or DMF as solvent gave the best result (Table 1, entries 8 and 10). So H_2O was chosen as the reaction solvent.[35]

Table 1. Optimization of reaction condition of compound **4b**

Yield (%)	*Time (h)*	*T (°C)*	*Solvent*	*Entry*
43	10	rt	MeCN	1
67	10	reflux	MeCN	2
27	10	rt	CH_2Cl_2	3
40	10	reflux	CH_2Cl_2	4
30	10	rt	THF	5
40	10	reflux	THF	6
61	10	rt	H_2O	7
74	8	reflux	H_2O	8
42	12	rt	DMF	9
75	10	reflux	DMF	10

The use of these optimal conditions to the reactions of different phenacyl bromide and thiocyanate derivatives afforded good yields of imidazo[2,1-*a*]isoquinolines with thioalkyl and aroyl groups presenting in positions 2 and 3 of the imidazole nucleus (Scheme 1, Table 2).

Table 2. Reaction of **1** with **2** and **3** in H_2O as the solvent.

Yield(%)	*R*	*X*	*4*
82	Me	H	a
74	Et	H	b
68	$PhCH_2$	H	c
83	Me	OMe	d
85	Et	OMe	e
78	$PhCH_2$	OMe	f
68	Et	Br	g
67	$PhCH_2$	Br	h
72	Me	Ph	i
76	Et	Ph	j
72	$PhCH_2$	Ph	k

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The ^{1}H-NMR spectrum of **4d** exhibited two sharp singlet signals readily recognized as arising from methylthio (δ= 2.69 ppm) and methoxy (δ= 3.95 ppm) protons. Two doublet signals at δ= 7.05 and δ=9.05 ppm (*J*=7.4 Hz) are observed for protons of nitrogen containing ring of isoquinoline moiety.

Aromatic protons of isoquinoline and methoxyphenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The proton-decoupled ^{13}C NMR spectrum of **4d** showed 18 distinct resonances in agreement with the proposed structure. The carbonyl group of **4d** appears at δ=185.5 ppm.

As the pharmacological profile of imidazo[1,2-*a*]pyridines has been shown to be critically dependent on the nature of substituents at 2 and 3 positions,[5, 36] it is expected that the above mentioned derivatives of imidazo[2,1-*a*]isoquinolines can show interesting pharmacological activities.

Mechanistically, it is conceivable that the reaction involves the initial formation of a nitrogen ylide **A** by the reaction of isoquinoline and phenacylbromide derivative followed by deprotonation in the presence of potassium carbonate as the base. This ylide intermediate then undergoes reaction with thiocyanate to produce **B** which leads to **C** by oxidation (Scheme 1).

In summary, a novel one-pot procedure for the synthesis of imidazo[2,1-*a*]isoquinolines has been reported, using isoquinoline, phenacylbromide derivatives and thiocyanates in aqueous medium. The notable advantages offered by this method are simple operation and environment friendly reaction conditions, high yields of products and cost effectiveness. Most significantly, this demonstrates the potential of water as an efficient promoter and provides much promise for the use of water in other chemical transformations. The conversion represents novel MCR and further studies are ongoing to explore additional transformations, feasible with these chemotypes.

EXPERIMENTAL

Chemicals were purchased from Merck and were used as received. Column chromatography was performed on silica gel (0.063-0.200 mm; Merck). IR Spectra: Shimadzu FTIR-4300 spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: Bruker DRX -500-Avance instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp; δ in ppm, J in Hz. EI-MS (70 eV): HP 5973 GC-MS instrument; in m/z. Elemental analyses (C, H, N): Heraeus CHN-O-Rapid analyzer. Melting points: Electrothermal 9200 apparatus.

***General procedure for the preparation of compound* 4a**. Isoquinoline (0.196 g, 1.5 mmol.) and phenacylbromide (0.3 g, 1.5 mmol.) were taken in water (10 mL) and the mixture was stirred at rt for 1 h. To this mixture methylthiocyanate (0.074 g, 1.0 mmol.) and potassium carbonate (0.28 g, 2.0 mmol.) were added and it was allowed to stir at reflux for 8 h. The reaction mixture filtered and purified by passing through a column of silica gel, eluting with 10%EtOAc in hexane to afford **4a** as yellow solid.

Compound (4a)

Yellow solid; Mp 150-151 °C; IR (KBr): 3130, 1596, 1575, 1508, 1429, 1352, 1217, 927 cm^{-1}; ^1H NMR ($CDCl_3$): δ=2.68 (s, 3H), 7.29 (d, *J*=7.4 Hz, 1H), 7.56 (m, 2H), 7.65 (m, 1H), 7.73 (m, 2H), 7.78 (m, 2H), 7.84 (m, 1H), 8.76 (m, 1H), 9.20 (d, *J*=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=15.6, 114.4, 122.4, 124.9,

125.0, 127.2, 128.6, 128.9, 129.1, 130.3, 131.6, 132.3, 140.2, 146.4, 153.8, 186.5 (C=O); MS (EI, 70ev): *m/z* (%) = 318 (M^+, 100), 285 (80), 257 (35), 227 (17), 213 (23), 167 (41), 149 (97), 128 (48), 105 (34), 77 (54); Anal. Calcd for $C_{19}H_{14}N_2OS$: C, 71.68; H, 4.43; N, 8.80. Found: C, 71.58; H, 4.47; N, 8.89.

Compound (4b)

Yellow solid; Mp 129-130 °C; IR (KBr): 3471, 2958, 1612, 1525, 1456, 1431, 1348, 1249, 1220, 925 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.38 (t, *J*=7.3 Hz, 3H), 3.30 (q, *J*=7.3 Hz, 2H), 7.28 (d, *J*=7.4 Hz, 1H), 7.56 (m, 2H), 7.64 (m, 1H), 7.73 (m, 2H), 7.79 (m, 2H), 7.84 (m, 1H), 8.76 (m, 1H), 9.17 (d, *J*=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=15.3, 27.1, 114.2, 122.4, 124.9, 125.0, 127.2, 128.6, 129.0, 129.1, 130.3, 131.6, 132.4, 140.2, 153.0, 186.0 (C=O); MS (EI, 70ev): *m/z* (%) = 332 (M^+, 69), 315 (15), 299 (88), 284 (36), 271 (24), 242 (15), 227 (43), 155 (12), 128 (43), 105 (100), 77 (87); Anal. Calcd for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43. Found: C, 72.38; H, 4.78; N, 8.46.

Compound (4c)

Yellow solid; Mp 134-135 °C; IR (KBr): 3058, 2924, 1610, 1573, 1510, 1433, 1348, 1274, 1222, 925 cm^{-1}; ^1H NMR ($CDCl_3$): δ=4.6 (s, 2H), 7.25 (m, 1H), 7.29 (m, 3H), 7.42 (m, 2H), 7.51 (m, 2H), 7.61 (tt, *J*=7.5, 1.3 Hz, 1H), 7.75 (m, 4H), 7.84 (m, 1H), 8.80 (m, 1H), 9.14 (d, *J*=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=37.0, 114.4, 122.48, 122.52, 124.9, 125.0, 127.2, 127.5, 128.7, 128.8, 129.0, 129.2, 129.6, 130.3, 131.6, 132.5, 138.6, 140.0, 146.3, 152.0, 186.5 (C=O); MS (EI, 70ev): *m/z* (%) = 394 (M^+, 20), 377 (2), 361 (26), 303 (10), 289 (10), 279 (34), 167 (79), 149 (100), 128 (11), 113 (25), 105 (24), 84 (53), 71 (47); Anal. Calcd for $C_{25}H_{18}N_2OS$: C, 76.12; H, 4.60; N, 7.10; Found: C, 76.02; H, 4.56; N, 7.17.

Compound (4d)

Yellow solid; Mp 140-142 °C; IR (KBr): 3043, 1595, 1510, 1436, 1348, 1251, 1170, 1028, 925 cm^{-1}; ^1H NMR ($CDCl_3$): δ=2.69 (s, 3H), 3.95 (s, 3H), 7.05 (d, *J*= 8.6 Hz, 2H), 7.26 (d, *J*= 7.0 Hz, 1H), 7.71 (m, 2H), 7.82 (d, *J*= 8.6 Hz, 2H), 7.84 (m, 1H), 8.75 (m, 1H), 9.06 (d, *J*= 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=15.7, 55.9, 114.2, 114.3, 122.5, 122.7, 124.77, 124.87, 127.2, 128.6, 130.1, 131.4, 131.6, 132.5, 146.2, 152.2, 163.6, 185.5 (C=O); MS (EI, 70ev): *m/z* (%) = 348 (M^+, 2), 279 (42), 167 (99), 149 (100), 135 (29), 121 (6), 113 (32), 104 (17), 83 (23), 71 (56); Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.95; H, 4.63; N, 8.04. Found: C, 68.83; H, 4.70; N, 8.12.

Compound (4e)

Yellow solid; Mp 123-125 °C; IR (KBr): 3138, 1593, 1433, 1409, 1346, 1257, 1172, 1026, 927 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.39 (t, *J*=7.3 Hz, 3H), 3.31 (q, *J*=7.3 Hz, 2H), 3.95 (s, 3H), 7.05 (d, *J*=8.5 Hz, 2H), 7.24 (d, *J*=7.4 Hz, 1H), 7.71 (m, 2H), 7.81 (m, 1H), 7.83 (d, *J*=8.5 Hz, 2H), 8.74 (m, 1H), 9.02 (d, *J*=7.4 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=15.4, 27.3, 55.9, 114.0, 114.2, 122.6, 123.0, 124.7, 124.9, 127.2, 128.5, 130.1, 131.4, 131.8, 132.5, 146.2, 151.2, 163.6, 185.6 (C=O); MS (EI, 70ev): *m/z* (%) = 362

(M^+, 20), 329 (19), 314 (7), 279 (17), 227 (12), 167 (38), 149 (100), 135 (37), 113 (11), 71 (22); Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.51; H, 5.05; N, 7.71.

Compound (4f)

Yellow solid; Mp 137-139°C; IR (KBr): 3240, 1616, 1608, 1508, 1454, 1344, 1218, 1172, 1028 cm^{-1}; ^1H NMR ($CDCl_3$): δ=3.93 (s, 3H), 4.59 (s, 2H), 7.0 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=7.4 Hz, 1H), 7.25 (m, 1H), 7.30 (m, 2H), 7.44 (d, *J*=7.2 Hz, 2H), 7.73 (m, 2H), 7.78 (d, *J*=8.7 Hz, 2H), 7.82 (m, 1H), 8.80 (m, 1H), 9.01 (d, *J*=7.4 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=37.2, 55.8, 114.2, 114.3, 122.6, 122.8, 124.7, 124.8, 127.2, 127.5, 128.6, 128.8, 129.6, 130.1, 131.4, 131.8, 132.3, 138.7, 146.0, 150.4, 163.6, 185.4 (C=O); MS (EI, 70ev): *m/z* (%) = 424 (M^+, 2), 391 (2), 296 (6), 279 (43), 267 (6), 191 (5), 167 (87), 149 (100), 132 (6), 113 (24), 71 (34); Anal. Calcd for $C_{26}H_{20}N_2O_2S$: C, 73.56; H, 4.75; N, 6.60. Found: C, 73.69; H, 4.67; N, 6.63.

Compound (4g)

Yellow solid; Mp 161-164°C; IR (KBr): 3176, 1602, 1585, 1508, 1427, 1344, 1221, 1066, 1015, 927cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.36 (t, *J*=7.5 Hz, 3H), 3.28 (q, *J*=7.5, 2H), 7.25 (d, *J*=7.5 Hz, 1H), 7.62 (dd, *J*=8.5, 2.0 Hz, 2H), 7.66 (dd, *J*=8.5, 2.0 Hz, 2H), 7.70 (m, 2H), 7.80 (m, 1H), 8.71 (m, 1H), 9.11 (d, *J*=7.5Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=14.9, 26.7, 114.0, 121.8, 121.9, 124.3, 124.6, 126.7, 126.8, 128.2, 130.0, 130.2, 131.2, 131.8, 138.4, 146.2, 152.8, 184.8 (C=O); MS (EI, 70ev): *m/z* (%) = 412 (M^+, ^{81}Br, 40), 410 (M^+, ^{79}Br, 39), 395 (9), 439 (12), 377 (36), 351 (9), 298 (34), 279 (35), 227 (72), 167 (87), 149 (100), 128 (41), 113 (29), 71 (52); Anal. Calcd for $C_{26}H_{20}N_2O_2S$: C, 58.40; H, 3.68; N, 6.81. Found: C, 58.51; H, 3.63; N, 6.88.

Compound (4h)

Yellow solid; Mp 157-158 °C; IR (KBr): 3161, 1605, 1500, 1433, 1377, 1272, 1174, 1066, 925 cm^{-1}; ^1H NMR ($CDCl_3$): δ=4.58 (s, 2H), 7.28 (m, 4H), 7.42 (d, *J*=7.2 Hz, 2H), 7.62 (m, 4H), 7.75 (m, 2H), 7.83 (m, 1H), 8.80 (m, 1H), 9.11 (d, *J*=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=37.0, 114.5, 122.3, 122.4, 124.8, 125.0, 127.2, 127.4, 127.6, 128.80, 128.83, 129.6, 130.5, 130.8, 131.6, 132.3, 138.5, 138.6, 146.4, 152.2, 185.2 (C=O); MS (EI, 70ev): *m/z* (%) = 474 (M^+, ^{81}Br, 12), 472 (M^+, ^{79}Br, 11), 441 (12), 439 (12), 360 (4), 302 (8), 289 (14), 279 (16), 167 (38), 149 (100), 128 (10), 113 (11), 91 (28), 71 (17). Anal. Calcd for $C_{25}H_{17}BrN_2OS$: C, 63.43; H, 3.62; N, 5.92. Found: C, 63.38; H, 3.69; N, 5.80.

Compound (4i)

Yellow solid; Mp 178-179 °C; IR (KBr): 3411, 2919, 1598, 1558, 1506, 1429, 1346, 1257, 1218, 925 cm^{-1}; ^1H NMR ($CDCl_3$): δ=2.7 (s, 3H), 7.29 (d, *J*=7.5 Hz, 1H), 7.45 (m, 1H), 7.53 (m, 2H), 7.74 (m, 4H), 7.80 (d, *J*=8.0 Hz, 2H), 7.84 (m, 1H), 7.88 (d, *J*=8.0 Hz, 2H), 8.77 (m, 1H), 9.18 (d, *J*=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=15.6, 114.4, 122.4, 122.5, 124.9, 125.0, 127.2, 127.71, 127.74, 128.5, 128.6, 129.3, 129.7, 130.3, 131.6, 138.9, 140.6, 145.2, 146.4, 153.5, 186.1 (C=O); MS (EI, 70ev): *m/z* (%) = 394 (M^+,

18), 361 (13), 441 (12), 333 (6), 279 (34), 231 (8), 181 (16), 167 (75), 149 (100), 128 (7), 113 (21), 71 (32); Anal. Calcd for $C_{25}H_{18}Br\,N_2OS$: C, 76.12; H, 4.60; N ,7.10. Found: C 76.20, H 4.62, N 7.15.

Compound (4j)

Yellow solid; Mp 127-129 °C; IR (KBr): 3138, 1615, 1552, 1508, 1454, 1348, 1251, 1220, 1151, 929 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.4 (t, *J*=7.3 Hz, 3H), 3.33 (q, *J*=7.3 Hz, 2H), 7.29 (d, *J*=7.4 Hz, 1H), 7.45 (m, 1H), 7.53 (m, 2H), 7.73 (m, 4H), 7.80 (d, *J*=8.2 Hz, 2H), 7.84 (m, 1H), 7.89 (d, *J*=8.2 Hz, 2H), 8.77 (m, 1H), 9.16 (d, *J*=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=15.4, 27.2, 114.2, 122.5, 122.8, 124.9, 125.0, 127.2, 127.6, 127.7, 128.4, 128.6, 129.3, 129.9, 130.3, 131.6, 138.8, 140.6, 145.2, 146.4, 152.6, 186.2 (C=O); MS (EI, 70ev): *m/z* (%) = 408 (M^+, 4), 394 (1), 375 (5), 279 (37), 227 (4), 181 (6), 167 (86), 149 (100), 113 (28), 71 (48); Anal. Calcd for $C_{26}H_{20}N_2OS$: C, 76.44; H, 4.93; N, 6.86. Found: C, 76.35; H, 4.85; N, 6.81.

Compound (4k)

Yellow solid; Mp 151-153 °C; IR (KBr): 3082, 1602, 1579, 1508, 1454, 1433, 1411, 1350, 1272, 1191, 929 cm^{-1}; ^1H NMR ($CDCl_3$): δ=4.6 (s, 2H), 7.23 (m, 1H), 7.29 (m, 3H), 7.43 (m, 3H), 7.52 (m, 2H), 7.74 (m, 6H), 7.84 (m, 3H), 8.81 (m, 1H), 9.12 (d, *J*=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=37.1, 114.4, 122.5, 122.7, 124.8, 124.9, 127.2, 127.5, 127.6, 127.7, 128.5, 128.7, 128.8, 129.3, 129.6, 129.9, 130.3, 131.6, 138.5, 138.6, 140.6, 145.3, 146.2, 151.7, 186 (C=O); MS (EI, 70ev): *m/z* (%) = 470 (M^+, 2), 437 (2), 415 (3), 279 (40), 237 (6), 181 (13), 167 (94), 149 (100), 132 (6), 113 (31), 104 (17), 71 (51); Anal. Calcd for $C_{31}H_{22}N_2OS$: C, 79.12; H, 4.71; N, 5.95. Found: C, 79.15; H, 4.80; N 6.03.

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