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FACILE AND GREEN METHOD FOR THE SYNTHESIS OF β-AMINOKETONE DERIVATIVES IN AQUEOUS MEDIA

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Three-component reaction of aromatic aldehyde, 2-naphthalenamine, and 1,2-diphenylethanone in aqueous media catalyzed by triethylbenzylammonium chloride (TEBAC) at 90°C gave 3-aryl-3-(naphthalen-2-ylamino)-1,2-diphenylpropan-1-one derivatives. The enol form of 1,2-diphenylethanone was tentatively proposed to participate in the formation of the products. Compared with previous methods, this three-component reaction has the advantages of green solvent, good yields, and operational simplicity.

Keywords: Aqueous media; 1,2-diphenylethanone; 2-naphthalenamine; TEBAC

INTRODUCTION

Compounds containing 1,3-amino-oxygenated functional moieties are ubiquitous to a variety of biologically important natural products and potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitors.[1] Of particular interest would be a facile method for the construction of 1,3-amido alcohols, as these molecules are versatile precursors for 1,3-amino alcohols and ligands for asymmetric catalysts.[2] It is noteworthy that aminotetraline derivatives manifest a number of important and therapeutically useful biological activities such as antidepressant, immunomodulatory, and antitumor activities.[3]

Despite this broad range of applications, only a few members of this family of compounds have been reported,[4] of which the main class was 1-amidoalkyl-2-naphthols and their derivatives. They are always catalyzed by Lewis or Brønsted acid catalysts such as Montmorillonite K10 clay,[5] $Ce(SO_4)_2$,[6] iodine,[7] $K_5CoW_{12}O_{40} \cdot 3H_2O$,[8] *p*-TSA,[9] sulfamic acid,[10] cation-exchanged resins,[11] and silica-sulfuric acid.[12] It should be noted that they were all performed in organic solvent; furthermore, only a few studies were concerned about 1,3-aminoketone,[13] so the development of a green method for 1,3-amino-oxygenated functional moieties was therefore of considerable synthetic importance.

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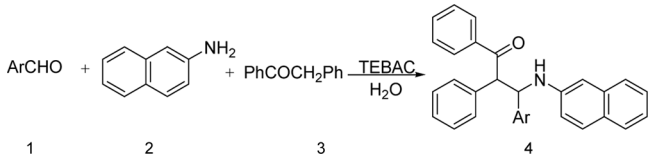
Development of organic reactions in water without use of harmful organic solvents is one of the current focuses, especially in the environmentally conscious focus today. Water has recently attracted considerable interest as a solvent for a large number of organic transformations[14] because it is abundant, nontoxic, and environmentally friendly compared to organic solvents. As part of our ongoing program to synthesize these active compounds in an environmentally friendly media,[15] herein we report a green synthesis of a series of 1,3-aminoketone derivatives in aqueous media catalyzed by triethylbenzylammonium chloride (TEBAC) by three-component reaction of aromatic aldehyde, 2-naphthalenamine, and 1,2-diphenylethanone.

RESULTS AND DISCUSSION

The treatment of aromatic aldehyde **1**, 2-naphthalenamine **2**, and 1,2-diphenylethanone **3** in water using 10 mol% TEBAC as phase-transfer catalysis at 90 °C afforded 3-aryl-3-(naphthalen-2-ylamino)-1,2-diphenylpropan-1-one derivatives **4** in good to high yields (Scheme 1).

Subsequently, the reaction of 3-nitrobenzaldehyde, 1,2-diphenylethanone, and 2-naphthalenamine was used as a model reaction to optimize the conditions. The reaction was first carried out in water in the absence of TEBAC. At room temperature, no reaction took place (Table 1, entry 1), and only a trace product of **3a** was observed by thin-layer chromatography (TLC) when the reaction temperature was raised to 90 °C (Table 1, entry 2). Similar reactions were then attempted in the presence of TEBAC with 1, 5, 10, and 20 mol% (Table 1, entries 5–8); just 10 mol% TEBAC at 90 °C in water gave the best yield. Greater amounts of the catalyst did not improve the yield. To find the optimum reaction temperature, the reaction was carried out in the presence of TEBAC with 10 mol% at room temperature, 50 °C, and 90 °C, resulting in the isolation of **4a** in trace, 62%, and 86% yield (Table 1, entries 3–5), respectively. Thus, 10 mol% TEBAC and a reaction temperature of 90 °C were chosen. In addition, $CH_3(CH_2)_{15}NMe_3Br$ and $CH_3(CH_2)_{11}SO_3Na$ (Table 1, entries 9 and 10) were also tested as the catalyst. In these cases, product **4a** was formed in slightly lower yields. The TEBAC could be reused for the synthesis of **4a** without significant loss of activity, and even in the fourth round, **4a** could be obtained in good yield (78%).

To extend the reaction (Scheme 1) to a library system, various kinds of aromatic aldehydes **1** were reacted with 1,2-diphenylethanone and 2-naphthalenamine, giving the corresponding 3-aryl-3-(naphthalen-2-ylamino) 1,2-diphenylpropan-1-one derivatives **4** successfully (Table 2). All of **1** gave expected products in good yields, either



Scheme 1. Reaction of aromatic aldehyde and 1,2-diphenylethanone and 2-naphthalenamine.

Table 1. Synthesis of **4a** in water under different reaction conditions[a]

Entry	Temp. (°C)	Cat. (mol%)	Catalyst	Yield[b] (%)
1	rt	0	—	0
2	90	0	—	trace
3	rt	10	TEBAC	trace
4	50	10	TEBAC	62
5	90	10	TEBAC	86
6	90	20	TEBAC	85
7	90	5	TEBAC	78
8	90	1	TEBAC	76
9	90	10	$CH_3(CH_2)_{15}NMe_3Br$	82
10	90	10	$CH_3(CH_2)_{11}SO_3Na$	83

[a]Reagents and conditions: **1** (0.302 g, 2 mmol), 2-naphthalenamine **2** (0.286 g, 2 mmol), 1,2-diphenylethanone **3** (0.392 g, 2 mmol), and TEBAC (0.091 g, 0.2 mmol), solvent (10 mL).
[b]Isolated yields.

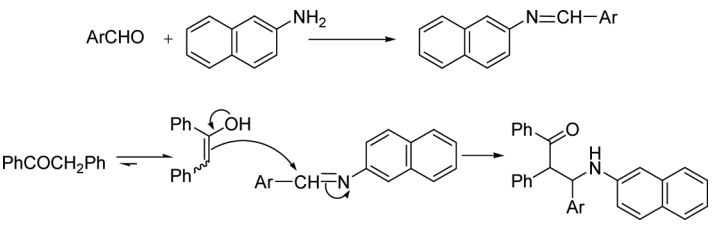
bearing electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkyl group, or alkoxyl group) under the same reaction conditions (Table 2). The other aromatic amines, such as aniline or *p*-toluidine, were also chosen as reactants to react with **1** and 1,2-diphenylethanone. However, they all gave a complicated system in this TEBAC-H_2O reaction condition.

Although the detailed mechanism of the reaction has not been clarified, the formation of 3-aryl-3-(naphthalen-2-ylamino)-1,2-diphenylpropan-1-one derivatives **4** could be explained by a possible mechanism as presented in Scheme 2. The condensation of aromatic aldehydes and 2-naphthalenamine may occur to generate Schiff base first, then the enol form of 1,2-diphenylethanone attacks the C=N double bond to give the final product. In this process, the action of TEBAC is as phase-transfer catalysis.

Table 2. Reactions of aromatic aldehyde and 1,2-diphenylethanone and 2-naphthalenamine in water[a]

Entry	Ar	Products	Time (h)	Yields (%)[b]
1	3-$NO_2C_6H_4$	**4a**	10	86
2	4-$NO_2C_6H_4$	**4b**	10	87
3	3-ClC_6H_4	**4c**	12	83
4	4-ClC_6H_4	**4d**	16	85
5	3-BrC_6H_4	**4e**	15	88
6	4-BrC_6H_4	**4f**	18	79
7	4-$CH_3C_6H_4$	**4g**	16	90
8	4-$CH_3OC_6H_4$	**4h**	15	89
9	3,4-$Cl_2C_6H_3$	**4i**	16	78
10	4-FC_6H_4	**4j**	14	89
11	3,4-$OCH_2OC_6H_3$	**4k**	16	92
12	3-FC_6H_4	**4l**	15	87

[a]Reagents and conditions: **1** (2 mmol), 2-naphthalenamine **2** (0.286 g, 2 mmol), 1,2-diphenylethanone **3** (0.392 g, 2 mmol), TEBAC (0.091 g, 0.2 mmol), and solvent (10 mL).
[b]Isolated yields.



Scheme 2. Possible mechanism of the reaction.

CONCLUSION

In conclusion, we found a facile and green method for the synthesis of 3-aryl-3-(naphthalen-2-ylamino)-1,2-diphenylpropan-1-one derivatives by three-component reaction of aromatic aldehyde, 2-naphthalenamine, and 1,2-diphenylethanone in aqueous media catalyzed by TEBAC at 90 °C. Compared with previous methods, this three-component reaction has the advantages of green solvent, good to high yields, and operational simplicity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Tensor 27 spectrometer in KBr pellets. ^{1}H NMR spectra were obtained from solution in dimethylsulfoxide (DMSO-d_6) or $CDCl_3$ with Me_4Si as internal standard using a Bruker 400 spectrometer. High-resolution mass spectrometric (HRMS) analyses were carried out using a Bruker Micro-TOF-Q-MS analyzer.

General Procedure for the Syntheses of 3-Aryl-3-(naphthalen-2-ylamino)-1,2-diphenylpropan-1-one Derivatives

A 50-mL flask was charged with aromatic aldehyde (2.0 mmol), 1,2-diphenylethanone (2.0 mmol, 0.392 g), 2-naphthalenamine (2.0 mmol, 0.286 g), TEBAC (0.2 mmol, 0.091 g), and water (10 mL). The reaction mixture was stirred at 90 °C for 10–18 h; the solid was isolated by filtration. The filtrate, together with TEBAC, could be used directly for the same reaction. The crude products were washed with water, purified by recrystallization from dimethylformamide (DMF) and water, and dried at 80 °C for several hours in a vacuum to give **4**.

Selected Data

1,2-Diphenyl-3-(naphthalen-2-ylamino)-3-(3-nitrophenyl)propan-1-one (4a). Mp 216–217 °C. IR (KBr): 3404, 3061, 1604, 1632, 1596, 1532, 1493, 1476, 1401, 1354, 1286, 1268, 1191, 822, 806, 754, 739, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 4.28 (s, 1H, NH), 5.00 (d, $J = 9.6$ Hz, 1H, CH), 5.45 (dd, $J = 9.6$ Hz, $J' = 3.2$ Hz, 1H, ArH), 6.55 (d, $J = 2.0$ Hz, 1H, ArH), 6.69 (dd, $J = 8.8$ Hz, $J' = 2.0$ Hz, 1H, ArH), 7.13–7.77 (m, 1H, ArH), 7.27–7.49 (m, 11H, ArH), 7.51

(d, $J = 8.8$ Hz, 1H, ArH), 7.58 (d, $J = 8.4$ Hz, 1H, ArH), 7.78 (d, $J = 7.6$ Hz, 1H, ArH), 7.92 (d, $J = 7.6$ Hz, 1H, ArH), 8.02 (dd, $J = 8.0$ Hz, $J' = 1.6$ Hz, 1H, ArH), 8.45 (s, 1H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{25}N_2O_3$ ($M + H^+$) 473.1865; found 473.1861.

1,2-Diphenyl-3-(naphthalen-2-ylamino)-3-(3-nitrophenyl)propan-1-one (4b). Mp 175–176 °C. IR (KBr): 3414, 3057, 1680, 1632, 1629, 1599, 1580, 1521, 1448, 1397, 1346, 1291, 1262, 1228, 1202, 1191, 1145, 1107, 1091, 981, 851, 831, 748, 700 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 5.35 (d, $J = 10.8$ Hz, 1H, CH), 5.61–5.66 (m, 1H, CH), 6.88 (b, 2H, ArH + NH), 6.98 (d, $J = 8.8$ Hz, 1H, ArH), 7.07–7.11 (m, 2H, ArH), 7.14–7.17 (m, 2H, ArH), 7.25–7.29 (m, 3H, ArH), 7.50–7.70 (m, 8H, ArH), 7.97 (d, $J = 8.0$ Hz, 2H, ArH), 8.13 (d, $J = 8.0$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{24}N_2O_3Na$ ($M + Na^+$) 495.1685; found 495.1681.

3-(3-Chlorophenyl)-1,2-diphenyl-3-(naphthalen-2-ylamino)propan-1-one (4c). Mp 222–223 °C. IR (KBr): 3410, 3053, 3023, 1669, 1633, 1595, 1578, 1531, 1492, 1474, 1488, 1401, 1354, 1285, 1268, 1206, 1191, 823, 805, 769, 740, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 4.16 (s, 1H, NH), 4.96 (d, $J = 9.2$ Hz, 1H, CH), 5.32 (d, $J = 9.2$ Hz, 1H, CH), 6.95 (d, $J = 2.0$ Hz, 1H, ArH), 6.67 (dd, $J = 8.8$ Hz, $J' = 2.0$ Hz, 1H, ArH), 7.11–7.20 (m, 3H, ArH), 7.28–7.36 (m, 5H, ArH), 7.42–7.59 (m, 9H, ArH), 7.78 (d, $J = 7.6$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{25}ClNO$ ($M + H^+$) 462.1625; found 462.1606.

3-(4-Chlorophenyl)-1,2-diphenyl-3-(naphthalen-2-ylamino)propan-1-one (4d). Mp 223–224 °C. IR (KBr): 3400, 3055, 3024, 1667, 1631, 1597, 1580, 1529, 1489, 1448, 1401, 1354, 1285, 1213, 1190, 1014, 852, 829, 815, 752, 742, 703 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 5.35 (t, $J = 10.0$ Hz, 1H, CH), 5.48 (d, $J = 10.8$ Hz, 1H, CH), 6.33 (d, $J = 10.0$ Hz, 1H, NH), 6.78 (s, 1H, ArH), 6.84 (dd, $J = 9.2$ Hz, $J' = 1.6$ Hz, 1H, ArH), 7.03–7.07 (m, 1H, ArH), 7.17–7.33 (m, 6H, ArH), 7.43–7.58 (m, 6H, ArH), 7.64 (d, $J = 8.8$ Hz, 2H, ArH), 7.69 (d, $J = 8.4$ Hz, 2H, ArH), 7.85 (d, $J = 7.6$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{25}ClNO$ ($M + H^+$) 462.1625; found 462.1604.

3-(3-Bromophenyl)-1,2-diphenyl-3-(naphthalen-2-ylamino)propan-1-one (4e). Mp 203–204 °C. IR (KBr): 3410, 3052, 3022, 1669, 1632, 1595, 1531, 1492, 1471, 1447, 1401, 1353, 1285, 1267, 1229, 1205, 1189, 1071, 995, 823, 805, 740, 701 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 5.34–5.38 (m, 1H, CH), 5.5 (d, $J = 11.2$ Hz, 1H, CH), 6.30 (d, $J = 9.6$ Hz, 1H, NH), 6.79–7.05 (m, 2H, ArH), 7.07–7.18 (m, 1H, ArH), 7.19–7.33 (m, 6H, ArH), 7.46–7.70 (m, 10H, ArH), 7.86 (d, $J = 7.6$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{25}BrNO$ ($M + H^+$) 506.1120; found 506.1117.

3-(4-Bromophenyl)-1,2-diphenyl-3-(naphthalen-2-ylamino)propan-1-one (4f). Mp 223–224 °C. IR (KBr): 3400, 3055, 3024, 1667, 1631, 1597, 1580, 1529, 1486, 1448, 1402, 1353, 1285, 1214, 1190, 1010, 829, 814, 751, 742, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 4.16 (s, 1H, NH), 4.95 (d, $J = 9.6$ Hz, 1H, CH), 5.32 (d, $J = 9.2$ Hz, 1H, CH), 6.56 (d, $J = 2.0$ Hz, 1H, ArH), 6.66 (dd, $J = 8.8$ Hz,

$J' = 2.0$ Hz, 1H, ArH), 7.12–7.16 (m, 1H, ArH), 7.27–7.38 (m, 7H, ArH), 7.42–7.50 (m, 8H, ArH), 7.58 (d, $J = 8.0$ Hz, 1H, ArH), 7.76 (d, $J = 8.4$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{25}BrNO$ ($M + H^+$) 506.1120; found 506.1116.

1,2-Diphenyl-3-(4-methylphenyl)-3-(naphthalen-2-ylamino)propan-1-one (4g). Mp 201–203 °C. IR (KBr): 3402, 3054, 3024, 1670, 1630, 1596, 1579, 1529, 1490, 1448, 1401, 1354, 1285, 1212, 1191, 851, 830, 813, 743, 697 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 2.11 (s, 3H, CH_3), 5.29–5.34 (m, 1H, CH), 5.48 (d, $J = 10.8$ Hz, 1H, CH), 6.23 (d, $J = 9.6$ Hz, 1H, NH), 6.77 (s, 1H, ArH), 6.84 (d, $J = 8.4$ Hz, 1H, ArH), 6.99–7.06 (m, 3H, ArH), 7.17–7.26 (m, 2H, ArH), 7.29–7.33 (m, 2H, ArH), 7.43–7.56 (m, 8H, ArH), 7.62 (d, $J = 7.6$ Hz, 2H, ArH), 7.85 (d, $J = 7.6$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{32}H_{28}NO$ ($M + H^+$) 442.2171; found 442.2171.

1,2-Diphenyl-3-(4-methoxyphenyl)-3-(naphthalen-2-ylamino)propan-1-one (4h). Mp 181–182 °C. IR (KBr): 3387, 3052, 2960, 2930, 1666, 1630, 1598, 1579, 1527, 1512, 1449, 1398, 1356, 1287, 1275, 1254, 1207, 1178, 1026, 828, 812, 744, 706, 696 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 3.60 (s, 3H, CH_3O), 5.28–5.33 (m, 1H, CH), 5.48 (d, $J = 11.2$ Hz, 1H, CH), 6.22 (d, $J = 10.0$ Hz, 1H, NH), 6.74–6.79 (m, 2H, ArH), 6.85 (d, $J = 7.6$ Hz, 1H, ArH), 7.03–7.06 (m, 1H, ArH), 7.17–7.33 (m, 4H, ArH), 7.43–7.63 (m, 11H, ArH), 7.85 (d, $J = 7.2$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{32}H_{28}NO_2$ ($M + H^+$) 458.2120; found 458.2117.

3-(3,4-Dichlorophenyl)-1,2-diphenyl-3-(naphthalen-2-ylamino)propan-1-one (4i). Mp 214–215 °C. IR (KBr): 3392, 3055, 3024, 1663, 1630, 1596, 1579, 1529, 1469, 1447, 1400, 1353, 1285, 1215, 1190, 1125, 1030, 902, 829, 815, 756, 742, 718, 705 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 5.37–5.42 (m, 1H, CH), 5.51 (d, $J = 10.4$ Hz, 1H, CH), 6.30 (d, $J = 10.0$ Hz, 1H, NH), 6.86–6.89 (m, 2H, ArH), 7.05–7.29 (m, 1H, ArH), 7.18–7.34 (m, 4H, ArH), 7.44–7.63 (m, 9H, ArH), 7.69 (dd, $J = 8.4$ Hz, $J' = 2.0$ Hz, 1H, ArH), 7.87 (d, $J = 7.2$ Hz, 2H, ArH), 7.99 (d, $J = 1.6$ Hz, 1H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{23}Cl_2NONa$ ($M + Na^+$) 518.1054; found 518.1050.

1,2-Diphenyl-3-(4-fluorophenyl)-3-(naphthalen-2-ylamino)propan-1-one (4j). Mp 201–202 °C. IR (KBr): 3399, 3055, 1666, 1633, 1598, 1531, 1507, 1448, 1403, 1356, 1285, 1269, 1227, 1206, 1190, 1157, 959, 851, 823, 804, 744, 703 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 5.35–5.40 (m, 1H, CH), 5.48–5.50 (m, 1H, CH), 6.29 (d, $J = 9.6$ Hz, 1H, NH), 6.80 (s, 1H, ArH), 6.86 (d, $J = 9.2$ Hz, 1H, ArH), 7.01–7.18 (m, 3H, ArH), 7.20–7.26 (m, 2H, ArH), 7.30–7.34 (m, 2H, ArH), 7.43–7.57 (m, 6H, ArH), 7.63–7.73 (m, 4H, ArH), 7.84 (d, $J = 7.2$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{25}FNO$ ($M + H^+$) 446.1920; found 446.1910.

1,2-Diphenyl-3-(3,4-methylenedioxylphenyl)-3-(naphthalen-2-ylamino) propan-1-one (4k). Mp 217–218 °C. IR (KBr): 3405, 3055, 3023, 1667, 1633, 1607, 1594, 1531, 1482, 1448, 1401, 1353, 1357, 1285, 1267, 1234, 1203, 1191, 1142, 1004, 950, 824, 804, 740, 702 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 5.27–5.32 (m, 1H,

CH), 5.45 (d, $J = 10.4$ Hz, 1H, CH), 5.85 (d, $J = 3.2$ Hz, 2H, OCH_2O), 6.18 (d, $J = 9.6$ Hz, 1H, NH), 6.73 (d, $J = 8.0$ Hz, 1H, ArH), 6.81–6.86 (m, 2H, ArH), 7.04–7.33 (m, 7H, ArH), 7.45–7.62 (m, 8H, ArH), 7.87 (d, $J = 7.2$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{32}H_{26}NO_3$ ($M + H^+$) 472.1909; found 472.1909.

1,2-Diphenyl-3-(3-fluorophenyl)-3-(naphthalen-2-ylamino)propan-1-one (4l). Mp 223–224 °C. IR (KBr): 3396, 3054, 1666, 1630, 1597, 1578, 1530, 1503, 1488, 1442, 1398, 1354, 1284, 1243, 1204, 1190, 1037, 929, 829, 812, 750, 743, 706 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): 5.37–5.42 (m, 1H, CH), 5.50 (d, $J = 10.4$ Hz, 1H, CH), 6.30 (d, $J = 10.0$ Hz, 1H, NH), 6.84–6.88 (m, 3H, ArH), 7.04–7.08 (m, 1H, ArH), 7.18–7.34 (m, 5H, ArH), 7.44–7.58 (m, 8H, ArH), 7.63 (d, $J = 8.0$ Hz, 2H, ArH), 7.86 (d, $J = 8.0$ Hz, 2H, ArH). HRMS (ESI, m/z): calcd. for $C_{31}H_{25}FNO$ ($M + H^+$) 446.1920; found 446.1914.

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