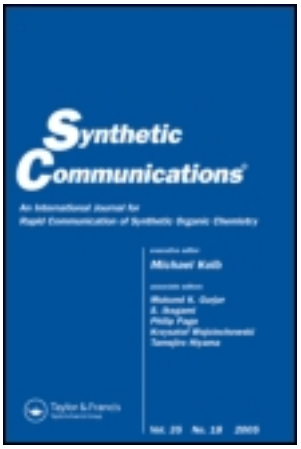

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Efficient, Solvent-Free, Microwave-Enhanced Condensation of 5,5-Dimethyl-1,3-cyclohexanedione with Aldehydes and Imines Using LiBr as Inexpensive, Mild Catalyst

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EFFICIENT, SOLVENT-FREE, MICROWAVE-ENHANCED CONDENSATION OF 5,5-DIMETHYL-1, 3-CYCLOHEXANEDIONE WITH ALDEHYDES AND IMINES USING LiBr AS INEXPENSIVE, MILD CATALYST

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Efficient, solvent-free, microwave-enhanced condensation of 5,5-dimethyl-1,3-cyclohexanedione with aldehydes using LiBr as catalyst affords xanthenediones. Imines gave only bis-5,5-dimethyl-1,3-cyclohexanediones at high power; a slightly longer period gave xanthenediones. In both types of reactions, the products are obtained in very good to excellent yields. The present protocol is inexpensive and ecofriendly.

Keywords: Aldehydes; 3-cyclohexanedione; 5-5-dimethyl-1; imines; LiBr; solvent-free; xanthenedions

INTRODUCTION

Xanthenediones are essential units of a variety of natural compounds and are also useful synthetic molecules. Above all these merits, they have shown important pharmacological properties.[1] This importance of these molecules has prompted synthetic chemists to search for efficient and facile methods for their production. Several methods have been reported to obtain xanthenedione derivatives conventionally, these are acid- or base-catalyzed reactions. In recent years, several other variants employing catalysts and conditions have been reported, such as Zn/I_2, solid acids, ionic liquids, organic solvents, microwave irradiation, sulfonic acid, and its derivatives.[2] Several of these already reported methods suffer from drawbacks such as long reaction time, expensive catalyst systems, harsh reaction conditions, impracticability, and poor yields. These limitations necessitated our search for a mild, inexpensive, and ecofriendly protocol for the synthesis of these molecules.

Use of LiBr in organic synthesis is of current interest because it is an inexpensive, nontoxic, readily available, mild Lewis acid catalyst. In view of these attractions, we and others have successfully employed this catalyst for Biginelli condensation, Ehrlich–Sachs reaction, Strecker reaction, Friedel–Crafts reaction, and preparation of acylals and xanthenes.[3] In most of these reported reactions, LiBr is almost neutral[4] and also does not form any corrosive or harsh by-products during

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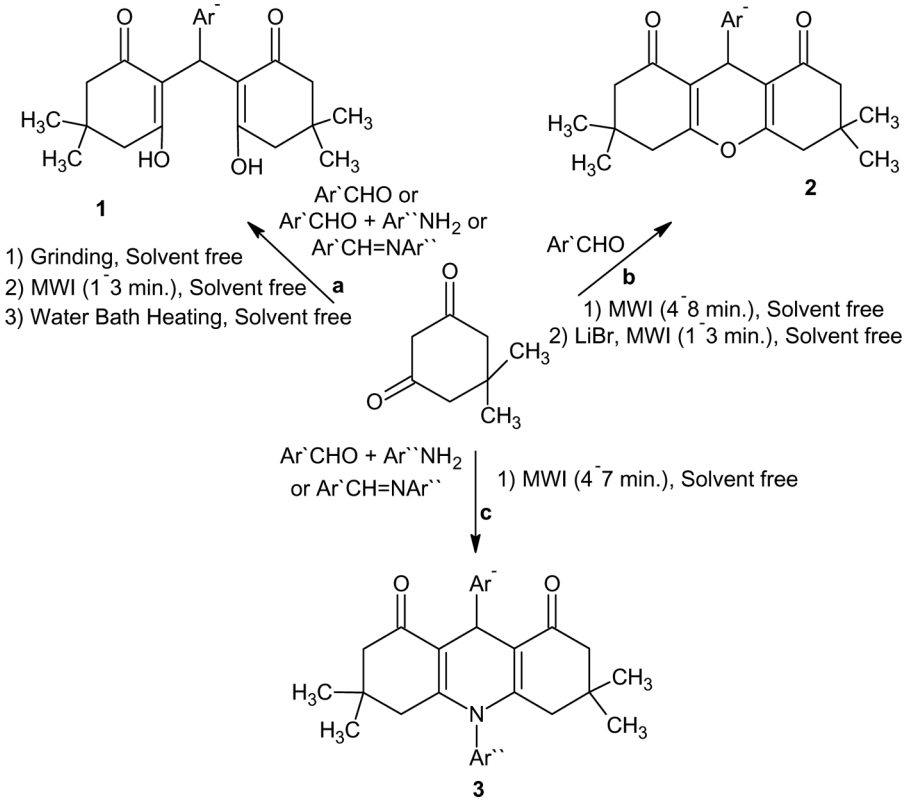

Scheme 1. Synthesis of xanthenediones derivatives.

aqueous workup, unlike other strong Lewis acids. In continuation of our own studies[3a–c] with LiBr, herein we report its use in the preparation of xanthenedione derivatives using aldehydes and aldeimines.

Table 1. Synthesis of bis-5,5-dimethyl-1,3-cyclohexanedione

Entry	Ar′	Ar″	Yield[a] A, A′, A″ (%)	Mp (°C) Found	Mp (°C) Reported
1a	C_6H_5	C_6H_5	95	191–193	188–190[2g]
1b	3,4-$(CH_3)_2C_6H_3$	4-ClC_6H_4	92	168–169	[2g]
1c	2-ClC_6H_4	3-ClC_6H_4	93	196–198	
1d	2,4-$Cl_2C_6H_3$	4-ClC_6H_4	95	186–188	188–190[2g]
1e	4-FC_6H_4	C_6H_5	86	185–187	
1f	3,4-$OCH_2OC_6H_3$	C_6H_5	88	165–167	168–170[2g]
1g	4-ClC_6H_4	4-ClC_6H_4	93	142–144	142–144[2g]
1h	3,4-$Cl_2C_6H_3$	4-ClC_6H_4	96	166–168	

[a]The products were characterized by comparison of their melting points and spectral (IR, ^{1}H NMR) data with those of authentic samples.

A, A′, and A″ are isolated yields (yields were nearly all the same in all cases) obtained from simple grinding, heating on a water bath, and MWI.

Table 2. Synthesis of xanthenediones

Entry	Ar′	Yield[a] (%)	Mp (°C) Found	Mp (°C) Reported
2a	C_6H_5	92	201–203	198–200[2e]
2b	4-$NO_2C_6H_4$	93	225–227	222–224[2e]
2c	3-$NO_2C_6H_4$	91	169–170	
2d	3,4-$OCH_2OC_6H_3$	92	224–225	216–218[2e]
2e	4-ClC_6H_4	93	228–229	230–231[2e]
2f	3-ClC_6H_4	90	181–183	
2g	2,4-$Cl_2C_6H_4$	90	252–253	

[a]The products were characterized by comparison of their melting points and spectral (IR, ^{1}H NMR) data with those of authentic samples.

To initate our investigation, we tried first simple grinding techniques using 1 mmol of benzaldehyde (1.06 mg) and 2 mmol of 5,5-dimethyl-1,3-cyclohexanedione (2.8 mg), and continued grinding at room temperature. On aqueous workup, this gave bis-5,5-dimethyl-1,3-cyclohexanedione products in 86–96% yields (Scheme 1a). The reaction is fairly general (see Table 1). In this protocol, heating on water bath for up to 1 h and use of LiBr did not yield xanthenediones.

Instead, bis-5,5-dimethyl-1,3-cyclohexanedione products were obtained. Also, if microwave irradiation (MWI) (1–3 min) is done without catalyst, bis-5,5-dimethyl-1,3-cyclohexanedione was formed and there was no xanthenediones in isolatable yield. A repeat of this experiment using LiBr 10 mol% under MWI afforded us the desired products in very good to excellent yields (Scheme 1b). Encouraged by this observation, we extended this reaction to other aldehydes to investigate the scope of this procedure (see Table 2). From the table, it is clear that the present procedure is fairly general.

Next, we turned to investigate this protocol using imines in place of aldehyde (Scheme 1a) with/without LiBr on water bath heating and MWI (1–3 min). Product **1** was obtained, and xanthenedions **3** were obtained after 4–7 min (Table 3). On simple grinding, the reaction did not proceed.

Table 3. Synthesis of 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones

Entry	Ar′	Product	Time (min)	Mp (°C) Found	Mp (°C) Reported	Yield (%)
1	C_6H_5	3a	6	264–266	262–263[3e]	75
2	4-$CH_3C_6H_4$	3b	5	294–295	285–287[3f]	88
3	4-$CH_3OC_6H_4$	3c	6	285–287	282–283[3f]	89
4	4-ClC_6H_4	3d	4.5	271–272	273–274[3e]	87
5	4-HOC_6H_4	3e	5	>300	>300[3f]	90
6	3-$NO_2C_6H_4$	3f	4	285–287	285–287[3f]	92
7	4-CNC_6H_4	3g	5	273–275	—	89
8	3,4-$Cl_2C_6H_4$	3h	4	>300	—	91

In conclusion, the present protocol employing a catalytic amount of LiBr is an efficient, simple, convenient, and mild strategy for the synthesis of xanthenediones and bis-5,5-dimethyl-1,3-cyclohexanedione derivatives. The catalyst LiBr is very mild, no harsh conditions are used and no corrosive by-products are formed during aqueous workup. The procedure is fairly general, high-yielding, and cost-effective. All these factors justify that it is superior over the existing methods.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Reagent-grade chemicals were purchased from a commercial source and used without further purification. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 (300-MHz) spectrometer using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

Some Typical General Methods

Simple grinding. Aldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclo-hexandione (2 mmol) were ground using a mortar and pestle for 60–90 min. Reaction completion was checked via TLC. Obtained product **1** was recrystallized from ethanol. The yield was 86–96% (Table 1). The same product was obtained using 10 mol% LiBr in this reaction, and yields are nearly the same as without catalyst (Table 1). In the case of imine and multicomponent reaction (aldehyde and p-toludine), the reaction did not proceed with simple grinding.

Water bath heating. Aldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclo-hexandione (2 mmol) was first mixed properly, after that, this reaction mixture was heated on a water bath up to 1 h. Obtained product **1** was recystallized from ethanol (Table 1). The same was also repeated with imines (1 mol) or multiple components (aldehyde and p-toludine, 1 mol equivalent) and 5,5-dimethyl-1,3-cyclo-hexandione (2 mmol). The obtained products were the same (Table 1). In these reactions, when we use LiBr (10 mol%), the obtained products were the same and the yield was nearly the same in all cases.

Microwave irradiation. The properly mixed reaction mixture of aldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclo-hexandione (2 mmol) was taken in a jointed conical flask, which was covered with a watch glass, and irradiated under MWI for 1–3 min. The obtained products are bis-5,5-dimethyl-1,3-cyclohexanediones (Table 1). When MWI continued for 4–8 min or when LiBr (10 mol%), was used under MWI for 1–3 min, the obtained products are xanthenediones (Table 2). Reaction completion was monitored via TLC. Products were recrystallized from ethanol. The reported yield was almost same as in the earlier case. The same was also repeated for imines (1 mol) or multiple components (benzealdehyde and p-toludine, 1 mol equivalent) and 5,5-dimethyl-1,3-cyclo-hexandione (2 mmol) under MWI for 1–3 min. The obtained products were the same xanthenediones derivatives (Table 1), but when we put the reaction mixture under MWI for 4–7 min,

uncatalyzed, the obtained products are 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones (Table 3).

Representative Spectral Data

Compound 1a. ^{1}H NMR ($CDCl_3$) d: 1.13 (s, 6H, 2 CH_3), 1.19 (s, 6H, 2 CH_3), 2.30–2.47 (m, 8H, 4 CH_2), 5.53 (s, 1H, CH), 6.52–6.81 (m, 5H, ArH), 9.44 (s, 1H, OH), 11.61 (s, 1H, OH); IR (KBr) v. 3000–2500, 2950, 2873, 1650, 1585, 1373, 1260, 1240, 1165, 1073, 950, 829, 787 cm^{-1}. Anal. calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.28; H, 7.75.

Compound 1b. ^{1}H NMR ($CDCl_3$) d: 0.92 (s, 6H, 2 CH_3), 1.01 (s, 6H, 2 CH_3), 2.26–2.36 (s, 8H, 4 CH_2), 5.53 (s, 1H, CH), 6.52–6.81 (m, 3H, ArH), 9.44 (s, 1H, OH), 11.61 (s, 1H, OH); IR (KBr) v. 3000–2500, 2958, 2889, 1584, 1501, 1464, 1448, 1369, 1313, 1266, 1253, 1165, 1124, 1065, 1044, 944, 912, 883, 821 cm^{-1}. Anal. calcd. for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.28, H, 8.01.

Compound 1c. ^{1}H NMR ($CDCl_3$) d: 1.06 (s, 6H, 2 CH3), 1.17 (s, 6H, 2 CH_3), 2.25–2.51 (m, 8H, 4 CH_2), 5.62 (s, 1H, CH), 7.09–7.39 (m, 4H, ArH), 9.76 (s, 1H, OH), 11.88 (s, 1H, OH); IR (KBr) v. 3000–2500, 2957, 2929, 1610, 1470, 1380, 1289, 1230, 1140, 1070, 987, 745 cm^{-1}. Anal. calcd. $C_{23}H_{27}ClO_4$: C, 68.56; H, 6.75. Found: C, 68.63; H, 6.59.

Compound 1d. ^{1}H NMR ($CDCl_3$) d: 1.06 (s, 6H, 2 CH_3), 1.28 (s, 6H, 2 CH_3), 2.06–2.41 (m, 8H, 4 CH_2), 5.57 (s, 1H, CH), 7.08–7.36 (m, 3H, ArH), 9.77 (s, 1H, OH), 11.88 (s, 1H, OH); 1 R (KBr) v. 3000–2500, 2956, 2872, 1608, 1559, 1468, 1396, 1290, 1229, 1100, 987, 861, 772 cm^{-1}. Anal. calcd. for $C_{23}H_{26}Cl_2O_4$: C, 63.16; H, 5.99. Found: C, 63.41; H, 5.76.

Compound 1e. ^{1}H NMR ($CDCl_3$) d: 1.06 (s, 6H, 2 CH3), 1.22 (s, 6H, 2 CH_3), 2.29–2.48 (m, 8H, 4 CH_2), 5.49 (s, 1H, CH), 6.93–7.06 (m, 4H, ArH), 9.77 (s, 1H, OH), 11.88 (s, 1H, OH); IR (KBr) v. 3000–2500, 2960, 2930, 2873, 1593, 1525, 1374, 1308, 1228, 1159, 870, 830, 800 cm^{-1}. Anal. calcd. for $C_{23}H_{27}FO_4$: C, 71.48; H, 7.04. Found: C, 71.63; H, 6.84.

Compound 1f. ^{1}H NMR ($CDCl_3$) d: 1.06 (s, 6H, 2 CH_3), 1.23 (s, 6H, 2 CH_3), 2.37–2.50 (m, 8H, 4 CH_2), 5.44 (s, 1H, CH), 5.89 (s, 2H, OCH_2O), 6.49–7.06 (m, 3H, ArH), 9.70 (s, 1H, OH), 11.90 (s, 1H, OH); IR (KBr) v. 3000–2500, 2950, 2875, 1600, 1480, 1370, 1301, 1250, 1230, 1040, 940, 860, 810 cm^{-1}. Anal. calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.63; H, 6.52.

Compound 1g. ^{1}H NMR ($CDCl_3$) d: 1.11 (s, 6H, 2 CH_3), 1.19 (s, 6H, 2 CH_3), 2.15–2.47 (m, 8H, 4 CH_2), 5.47 (s, 1H, CH), 7.01–7.32 (m, 4H, ArH), 10.0 (s, 1H, OH), 11.95 (s, 1H, OH); IR (KBr) v. 3000–2500, 2950, 2872, 1605, 1518, 1360, 1260, 1230, 1110, 1060, 881, 810, 780 cm^{-1}. Anal. calcd. for $C_{23}H_{27}ClO_4$: C, 68.56; H, 6.75. Found: C, 69.04; H, 6.45.

Compound 1h. ^{1}H NMR ($CDCl_3$) d: 0.97 (s, 6H, 2 CH_3), 1.09 (s, 6H, 2 CH_3), 2.06 (s, 6H, 2 CH_3), 2.25–2.38 (m, 8H, 4 CH_2), 5.97 (s, 1H, CH), 7.05–7.29 (m, 3H, ArH), 10.11 (s, 1H, OH), 11.93 (s, 1H, OH); IR (KBr) v. 3000–2500, 2957, 2869,

1715, 1607, 1562, 1471, 1403, 1351, 1294, 1240, 1169, 1140, 1099, 1070, 1026, 1014, 985, 935, 896, 876, 838, 810, 694 cm^{-1}. Anal. calcd. for $C_{23}H_{26}Cl_2O_4$: C, 63.16; H, 5.99. Found: C, 63.58; H, 5.47.

Compound 2a. ^{1}H NMR ($CDCl_3$) d: 0.98 (s, 6H, 2 CH_3), 1.12 (s, 6H, 2 CH_3), 2.20–2.45 (m, 8H, 4 CH_2), 4.66 (s, 1H, CH), 7.21–7.40 (m, 5H, ArH); IR (KBr) v. 3030, 2980, 1685, 1670, 1470, 1360, 1200, 1170, 1140, 1005, 740, 700 cm^{-1}. Anal. calcd. for $C_{23}H_{26}O_3$: C, 78.83; H, 7.47. Found: C, 78.96; H, 7.40.

Compound 2b. ^{1}H NMR ($CDCl_3$) d: 0.99 (s, 6H, 2 CH_3), 1.12 (s, 6H, 2 CH_3), 2.01–2.21 (m, 8H, 4 CH_2), 4.76 (s, 1H, CH), 7.50–7.63 (m, 2H, ArH), 8.06–8.18 (m, 2H, Ar); IR (KBr) v. 3035, 2980, 1660, 1650, 1630, 1520, 1360, 1340, 1200, 1070, 1040, 1000, 870, 830 cm^{-1}. Anal. calcd. for $C_{23}H_{25}NO_5$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.91; H, 6.60; N, 3.29.

Compound 2c. ^{1}H NMR ($CDCl_3$) d: 1.02 (s, 6H, 2 CH_3), 1.13 (s, 6H, 2 CH_3), 2.21–2.53 (m, 8H, 4 CH_2), 4.85 (s, 1H, CH), 7.43 (s, 1H, ArH), 7.88–7.95 (m, 3H, ArH); IR (KBr) v. 3030, 2980, 1680, 1675, 1625, 1535, 1365, 1340, 1210, 1175, 1145, 1005, 830, 765, 730, 700 cm^{-1}. Anal. calcd. for $C_{23}H_{25}NO_5$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.91; H, 6.50; N, 3.39.

Compound 2d. ^{1}H NMR ($CDCl_3$) d: 1.00 (s, 6H, 2 CH_3), 1.10 (s, 6H, 2 CH_3), 2.06–2.31 (m, 8H, 4 CH_2), 4.58 (s, 1H, CH), 5.90 (s, 2H, OCH_2O), 6.69–6.78 (m, 3H, ArH); IR (KBr) v. 2980, 1720, 1630, 1565, 1510, 1490, 1440, 1380, 1360, 1320, 1270, 1230, 1040, 940, 920, 890, 810, 790 cm^{-1}. Anal. calcd. for $C_{24}H_{26}O_5$: C, 73.07; H, 6.64. Found: C, 73.18; H, 6.76.

Compound 2e. ^{1}H NMR ($CDCl_3$) d: 0.98 (s, 6H, 2 CH_3), 1.10 (s, 6H, 2 CH_3), 2.22–2.50 (m, 8H, 4 CH_2), 4.64 (s, 1H, CH), 7.26–7.42 (m, 4H, ArH); IR (KBr) v. 3030, 2980, 1680, 1660, 1620, 1490, 1480, 1360, 1200, 1170, 1140, 1090, 1010, 1000, 850, 840 cm^{-1}. Anal. calcd. for $C_{23}H_{25}ClO_3$: C, 71.77; H, 6.54. Found: C, 71.88; H, 6.44.

Compound 2f. ^{1}H NMR ($CDCl_3$) d: 1.02 (s, 6H, 2 CH_3), 1.12 (s, 6H, 2 CH_3), 2.30–2.49 (m, 8H, 4 CH_2), 4.74 (s, 1H, CH), 7.11–7.25 (m, 4H, ArH); IR (KBr) v. 3030, 1685, 1660, 1620, 1490, 1475, 1365, 1200, 1170, 1136, 1090, 1010, 1000, 850, 840 cm^{-1}. Anal. calcd. for $C_{23}H_{25}ClO_3$: C, 71.77; H, 6.54. Found: C, 71.92; H, 6.41.

Compound 2g. ^{1}H NMR ($CDCl_3$) d: 1.03 (s, 6H, 2 CH_3), 1.12 (s, 6H, 2 CH_3), 2.21–2.46 (m, 8H, 4 CH_2), 4.95 (s, 1H, CH), 7.16 (s, 1H, ArH), 7.39 (d, $J = 4$ 8.4 Hz, 2H, ArH), IR (KBr) v. 3035, 2980, 1685, 1660, 1633, 1490, 1485, 1410, 1360, 1210, 1195, 1155, 1100, 1000, 850, 770 cm^{-1}. Anal. calcd. for $C_{23}H_{24}Cl_2O_3$: C, 65.87; H, 5.73. Found: C, 65.94; H, 5.60.

Compound 3g. Pale yellow solid. Mp 273–275°C. IR (KBr): $\nu_{max} = 3035$, 2957, 2872, 2360, 2224, 1633, 1605, 1574, 1513, 1471, 1361, 1300, 1277, 1224, 1176, 1144, 1123, 1019, 1002, 853, 568, 527 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (s, 6H), 0.95 (s, 6H), 1.84 (d, $J = 17.4$ Hz, 2H), 2.08 (d, $J = 17.4$ Hz, 2H), 2.08 (d, $J = 17.4$, 2H), 2.15 (d, $J = 17.4$, 2H), 2.49 (s, 3H), 5.30 (s, 1H), 7.08 (d, $J = 7.8$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 2H), 7.54 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, all 1C unless indicated): δ 21.4, 26.8 (2C), 29.7 (2C), 32.5 (2C), 33.8, 41.9 (2C), 50.2

(2C), 109.7, 113.6 (2C), 119.4, 128.8, 128.9 (2C), 129.5, 130.9 (2C), 132.0, 132.1 (2C), 136.1, 139.9, 150.7, 151.7, 195.8 (2C); HR-MS (EI-TOF): m/z = 464.2460 [M^+], calcd. for $C_{31}H_{32}N_2O_2$: 464.2464.

Compound 3h. Pale yellow solid. Mp > 300°C. IR (KBr): $\nu_{max} = 3035$, 2958, 2871, 1639, 1574, 1512, 1468, 1424, 1360, 1301, 1262, 1219, 1177, 1144, 1025, 881, 833, 753, 673, 571, 527 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (s, 6H), 0.95 (s, 6H), 1.84 (d, $J = 17.3$ Hz, 2H), 2.07 (d, $J = 17.3$ Hz, 2H), 2.13 (d, $J = 16.4$ Hz, 2H), 2.21 (d, $J = 16.4$ Hz, 2H), 2.48 (s, 3H), 5.22 (s, 1H), 7.07 (d, $J = 8.4$ Hz, 2H), 7.32–7.36 (m, 4H), 7.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, all 1C unless indicated): δ 21.4, 26.8 (2C), 29.7 (2C), 32.45 (2C), 32.51, 41.8 (2C), 50.2 (2C), 113.8 (2C), 127.7, 128.7, 129.6 (br), 129.7 (br), 130.0 (2C), 131.0 (br), 131.7 (br), 131.9, 136.1, 139.8, 146.7, 150.6 (2C), 195.8 (2C); HR-MS (EI-TOF): m/z = 507.1723 [M^+], calcd. for $C_{30}H_{31}NO_2Cl_2$: 507.1732.

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