An Efficient Ultrasound-Assisted Synthesis of *N*-Alkyl Derivatives of Carbazole, Indole, and Phenothiazine

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Heterocyclic compounds bearing an acidic hydrogen atom attached to nitrogen such as carbazole, indole, and phenothiazine can be efficiently alkylated in DMSO or *N*,*N*-DMF under ultrasonic irradiation in the presence of potassium hydroxide as a base. In almost all cases, a dramatic reduction of the reaction time results and a clear yield increase accompanied by an improved quality of the products occurs.

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INTRODUCTION

Over the course of the last decades, N-heterocyclic compounds containing carbazole, indole, and phenothiazine units have gained much attention for their wide-ranging implications in chemistry, biology, and materials science [1]. Nalkylcarbazole, N-alkylindole, and N-alkylphenothiazine are the main intermediates used in these fields. Despite their versatility, available routes for their synthesis are limited. One of the most practical and widely used routes for the synthesis of these compounds is direct alkylation of carbazole, indole, or phenothiazine with an alkylation agent. They are generally accomplished by the treatment of these compounds with an appropriate base such as KOH [2], NaOH [3], NaH [4], and K₂CO₃ [5], followed by reaction of the resulting salt with an alkylation agent in various solvents, such as DMSO [6], DMF [7], THF [8], and HMPT (Hexamethyl phosphoryl triamide) [9], and others. In an early report, Guida found that the N-alkylation of heterocyclic compounds can be accomplished in diethyl ether via a phase-transfer process in which 18crown-6 is used as the catalyst and potassium tert- butoxide is used as the base [10]. Recently, Hayat et al. reported on the N-alkylation of nitrogen heterocycles with alkyl halide using CsF/Celite in acetonitrile [11]. However, some of these methods are limited by low yields or long reaction time. Therefore, the development of a mild and efficient method of N-alkylation of heterocyclic compounds bearing an acidic hydrogen atom attached to nitrogen is still a major challenge in organic synthesis. Most recently, Le [12] and Jorapur [13] demonstrated N-alkylation of heterocyclic compounds in ionic liquid, respectively; some excellent results were obtained; however, the expensive price and inconvenience of ionic liquids may become the biggest obstacle to its wide application.

Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the last three decades [14]; compared with traditional methods, the procedure is more convenient. A large number of organic reactions can be carried out in higher yield, shorter reaction time, or milder conditions under ultrasonic irradiation. Because of the absence of reported ultrasonic-assisted Nalkylation of nitrogen heterocycles and our general interest in the development of clean chemical processes, herein, we wish to report an improved procedure for the N-alkylation of carbazole, indole, and phenothiazine. Under ultrasound irradiation, a variety of *N*-alkyl derivatives of carbazole, indole, and phenothiazine were prepared with mild reaction conditions, short reaction time, and moderate to high yields (Scheme 1).

RESULTS AND DISCUSSION

Ultrasound-accelerated chemical reactions are well known and proceed via the formation and adiabatic collapse of the transient cavitation bubbles [14]. In previous studies, we found that the ultrasound can accelerate the Zincke reaction [16]. As a continuation of our research interest in developing synthetic protocols using ultrasound irradiation, a laboratory ultrasonic cleaning bath was used for the N-alkylation of heterocyclic compounds bearing an acidic hydrogen atom attached to nitrogen. In a recent report [17], Qin developed a simple approach to synthesize *N*-ethylcarbazole by using dipolar aprotic solvent DMF as reaction medium, and using conventional magnetic stirring, the reaction of carbazole with bromoethane gave the desired product in 92.4% yield after 10 h. Although the aforementioned method provided excellent yield, the reaction time is indeed long. Thus, to shorten the reaction time and to evaluate the effect of ultrasonic irradiation, the reaction of carbazole with bromoethane in DMF with KOH as a base was selected as a model reaction under ultrasound



irradiation conditions (Table 1). Initially, the effect of ultrasonic power was investigated. To our surprise, only after 6 min, the excellent product yield 98% was obtained with the ultrasonic power 90 W, irradiation frequency 40 kHz, and the reaction temperature 35°C (Table 1, entry 4); it is apparent that the ultrasound can accelerate the reaction significantly. To search the better reaction conditions and because the nucleophilic substitution reactions are strongly dependent on the polarity of the reaction

Table 1

Effect of solvent and the ultrasonic power on the N-alkylation reaction of carbazole with bromoethane.

Entry	Power (W)	Solvent	Irradiation time	Yield (%) ^a
1	40	DMF	30 min	57
2	60	DMF	30 min	64
3	80	DMF	30 min	82
4	90	DMF	6 min	98
5	100	DMF	6 min	89
6	90	DMSO	3 min	99
7	90	PEG-400	3 h	67
8	90	H_2O	3 h	ND
9	90	THF	3 h	59
10	90	\land	3 h	75
11	90		3 h	70
		NN BF4		
12	90	BF4 OH	3 h	56
13 14 ^b	80	DMSO	3 min 3 h	86 81

Conditions: The reactions were run with carbazole (5 mmol), KOH (10 mmol), bromoethane (10 mmol), solvent (10 mL), and the reaction temperature 35° C; the reaction progress was monitored by TLC.

^aRefers to work-up yield.

^bConventional method with magnetic stirring.

medium, several polar solvents such as DMSO, PEG-400, THF, H₂O, and three ionic liquids [N-ethylpyridinium tetrafluoroborate, N-butylpyridinium tetrafluoroborate, and *N*-(2-hydroxypropyl)-pyridinium tetrafluoroborate] were explored; the results are summarized in Table 1. It can be seen from Table 1 that the reaction performed in PEG-400, THF, and three ionic liquids afforded comparatively low yields at long reaction time. Whereas when water was chosen as the reaction medium, the desired product is not observed. Under the same conditions, however, the best result (yield 99%, reaction time 3 min; Table 1, entry 6) was obtained in dipolar aprotic solvent DMSO. For the same reaction, if no ultrasonic irradiation, only 81% of yield was obtained after 3 h (Table 1, entry 14). The aforementioned results clearly demonstrate that the N-alkylation of carbazole with bromoethane in DMF or DMSO can be greatly accelerated by ultrasonic irradiation. Main explanations for the acceleration under the ultrasonic irradiation may be based on two effects: (i) vigorous agitation makes the molecular reaction interact very well; and (ii) momentary high temperature and great pressure generated by the bubble collapse prompt the reaction greatly.

To test the generality of this approach, various alkyl halides were allowed to react with carbazole in DMF or DMSO. As is evident from Table 2, the ultrasound-assisted N-alkylation reactions preceded smoothly; most of the alkyl halides can be substituted with moderate to high yield. When using 0.5 equiv of 1,4-dibromobutane or 1,3-dibromobutane as alkylation agent, disubstituted products 1,4-di(carbazol-9-yl) butane and 1,3-di(carbazol-9-yl)propane were obtained with yield 90 and 89%, respectively (Table 2, entries 8 and 9). However, when using 2 equiv of 1,4-dibromobutane in the S_N2 reaction of carbazole with 1,4-dibromobutane, the reaction stopped at the monosubstituted stage, and only monosubstituted compound N-(4-bromobutyl) carbazole was obtained with the yield of 92% in DMSO after 80 min (Table 2, entry 7). The reasons for this may be attributed to two factors: one is the steric effect on the substrate alkyl halide, N-(4-bromobutyl) carbazole, is more hindered, and then, 1,4-dibromobutane, the nucleophile, can easily approach an electrophilic carbon atom of 1,4-dibromobutane and produce the product N-(4-bromobutyl) carbazole. For the N-(4-bromobutyl) carbazole, the further approach is

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Table 2				
Alkylation of carbazole with different a	alkyl halides in DMSO and DMF.			

Entry	Alkyl halide	Product	Irradiation time (min)	Solvent	Yield (%) ^a
1	BrCH ₂ CH ₃		6 3	DMF DMSO	98 99
2	Br(CH ₂) ₃ CH ₃	CH ₂) ₃ CH ₃	10 6	DMF DMSO	97 98
3	Br(CH ₂) ₉ CH ₃	N ICH2)aCH3	150 110	DMF DMSO	90 95
4	Br		50 30	DMF DMSO	96 98
5	CICH ₂ CH ₂ OH	CT NOH	240 180	DMF DMSO	76 87
6	Br		60 35	DMF DMSO	94 97
7	Br(CH ₂) ₄ Br	(CH ₂) ₃ CH ₂ Br	125 80	DMF DMSO	88 92
8 ^b	Br(CH ₂) ₄ Br	N-(CH ₂) ₄ -N	90 75	DMF DMSO	87 90
9 ^b	Br(CH ₂) ₃ Br	N-(CH ₂) ₃ -N	130 100	DMF DMSO	87 89
10 ^b	BrCH ₂ CH ₂ Br	N-(CH ₂) ₂ -N	240 240	DMF DMSO	Trace Trace

Conditions: All reactions except entries 8–10 were run with carbazole (5 mmol), KOH (10 mmol), and alkyl halide (10 mmol) in DMSO (10 mL) or DMF (10 mL) with the reaction temperature 35°C and the ultrasonic power 90 W; ^aRefers to work-up yield; ^bFor entries 8–10, the amount of alkyl halide is 0.25 mmol.

hindered. Another factor is the concentration of alkyl halide; when 2 equiv of 1,4-dibromobutane was used, the concentration of 1,4-dibromobutane is far higher than the concentration of the monosubstituted product *N*-(4-bromobutyl) carbazole; thus, the reaction of carbazole with 1,4-dibromobutane is preferred, and the monosubstituted compound is the main product. With the less reactive alkylation agent 2chloroethanol, longer reaction times are required (Table 2, entry 5), and for the alkylation agent 1,2-dibromoethane, 1,2-dichloroethane, and 1,3-dichloro-2,2-bis(chloromethyl) propane, trace or no product was detected.

Aiming to increase the scope of our methodology, we next exploited our method to other heterocycles possessing acidic hydrogen such as indole and phenothiazine. The results presented in Tables 3 and 4 suggest that N-alkylation of indole and phenothiazine with a variety of alkylation agents proceeds smoothly with yields ranging from good to excellent. In early reports [18], some C-alkylation is observed when allylic or benzylic halides were used as alkylation agents for the N-alkylation of indole. To further confirm the advantages of our methodology, the allyl and benzyl bromides were used as alkylation agents (Table 3, entries 4 and 5); according to TLC, NMR, and GC analyses, exclusive N-alkylation of indole can be produced with high yield. It is noteworthy that the reactions of 0.5 equiv of 1,4-dibromobutane with indole (Table 3, entry 6) and phenothiazine (Table 4, entry 6) gave disubstituted products 1,4-di(indol-1-yl)butane and 1,4-di(phenothiazin-10-yl)butane with yield 84and 81%, respectively. Finally, as we expected, when *tert*-butyl chloride was selected as alkylating agent, no product was detected, and many bubbles were produced in the process of ultrasonic irradiation. It may be caused by the elimination reaction of *tert*-butyl chloride in the presence of KOH.

CONCLUSIONS

In summary, we have succeeded in developing the Nalkylation of carbazole, indole, and phenothiazine with a variety of alkylation agents under ultrasonic conditions. Under the optimized conditions of ultrasonic irradiation, a series of N-substituted derivatives of carbazole, indole,

Entry	Alkyl halide	Product	Irradiation time (min)	Yield (%) ^a
1	BrCH ₂ CH ₃		20	96
2	Br(CH ₂) ₃ CH ₃	CCH ₂) ₃ CH ₃	50	94
3	Br(CH ₂) ₉ CH ₃	CH ₂) ₉ CH ₃	160	56
4	Br		100	87
5	Br		90	92
6 ^c	Br(CH ₂) ₄ Br	N-(CH ₂) _{4-N}	120	84

 Table 3

 Alkylation of indole with different alkyl halides in DMSO.

Conditions: All reactions except entry 6 were run with indole (5 mmol), KOH (10 mmol), alkyl halide (10 mmol) in DMSO (10 mL) with the reaction temperature 35° C and the ultrasonic power 90 W;

^aRefers to work-up yield;

^bFor entry 6, the amount of alkyl halide is 0.25 mmol.

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Entry	Alkyl halide	Product	Irradiation time (min)	Yield (%) ^a
1	BrCH ₂ CH ₃	N N N N N N N N N N N N N N N N N N N	25	96
2	Br(CH ₂) ₃ CH ₃	S N N	40	94
3	Br(CH ₂) ₉ CH ₃	S N (CH ₂) ₉ CH ₃	100	83
4	Br		120	86
5	Br		180	78
6 ^c	Br(CH ₂) ₄ Br	S N-(CH ₂) ₄ -N S	90	81

 Table 4

 Alkylation of phenothiazine with different alkyl halides in DMSO

Conditions: All reactions except entry 6 were run with phenothiazine (5 mmol), KOH (10 mmol), and alkyl halide (10 mmol) in DMSO (10 mL) with the reaction temperature 35° C and the ultrasonic power 90 W;

^aRefers to work-up yield;

^bFor entry 6, the amount of alkyl halide is 0.25 mmol.

and phenothiazine were prepared and characterized by ¹H and ¹³C NMR spectral, and elemental analyses. This method displays dramatically reduced reaction time compared with conventional methods and also affords the desired products in moderate to high yields and purity.

EXPERIMENTAL

Melting points were measured on WRS-1B digital melting point meter (Shanghai Jingke, Shanghai, China) and are uncorrected. ¹H NMR and ¹³C NMR spectra were measured on a Bruker Avance 500 MHz spectrometer (Bruker Corporation, Switzerland) using TMS as an internal standard in CDCl₃ (Supporting Information). The elemental analyses were performed in the EuroEA3000 element analyzer (Erba Corporation, Italy). Sonication was performed in Kunshan KQ-400KDE ultrasonic cleaner (with frequency 40 KHz and maximum output power 400 W; Kunshan Ultrasonic Instrument Corporation, Suzhou, China), the reaction flasks were located in the maximum energy area in the water bath, where the surface of reactants is slightly lower than the level of the water, and the reaction temperature was controlled by exchange of the water in ultrasonic cleaning bath. Analytical TLC was carried out using MN Kieselgel G/UV₂₅₄ (Art.816320) glass-backed plates (Qingdao Marine, Qingdao, China). All chemical reagents were obtained from commercial suppliers and used without further purification. Ionic liquids *N*-ethylpyridinium tetrafluoroborate, *N*-butylpyridinium tetrafluoroborate, and *N*-(2-hydroxypropyl)-pyridinium tetrafluoroborate were prepared according to the literature [19].

General procedure for the synthesis of N-substituted carbazole, indole, and phenothiazine. To a solution containing N-heterocyclic (5 mmol) in DMSO (10 mL) was added KOH (10 mmol); the mixture was stirred at RT for 20 min. Then, the appropriate alkyl chloride or alkyl bromide (10 mmol) was added, and the reaction mixture was irradiated by 40 kHz ultrasound at 35° C. The reaction progress was monitored by

TLC. Upon completion, the reaction mixture was partitioned with Et_2O (40 mL) and water (30 mL), the organic phase was washed with brine (2 × 30 mL) and dried over anhydrous Na₂SO₄, and removal of solvent on a rotary vacuum evaporator to yield the almost pure object product was carried out. Further purification can be achieved by recrystallization from ethanol or by column chromatography using petroleum ether–ethyl acetate (5:1) as eluent.

N-Ethylcarbazole (Table 2, entry 1) [3]. White solid, mp 68–69°C (Lit. mp 67–68°C); ¹H NMR (500 MHz, CDCl₃): $\delta = 8.06$ (d, J = 5.0 Hz, 2H), 7.42 (d, J = 5.0 Hz, 2H), 7.33 (d, J = 10.0 Hz, 2H), 7.20–7.18 (t, J = 5.0 Hz, 2H), 4.27–4.22 (q, J = 7.0 Hz, 2H), 1.33(t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 139.8$, 125.5, 122.89, 120.3, 118.7, 108.3, 37.3, 13.7.

N-Butylcarbazole (Table 2, entry 2) [3]. White solid; mp 59–60°C (Lit. mp 58–59°C); ¹H NMR (500 MHz, CDCl₃): $\delta = 8.09$ (d, J = 12.5 Hz, 2H), 7.47–7.43 (q, J = 12 Hz, 4H), 7.40–7. 19(m, 2H), 4.29 (t, J = 12.0 Hz, 2H), 1.89–1.79 (m, 2H), 1.43–1.35 (m, 2H), 0.93 (t, J = 12 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 140.4$, 125.5, 122.8, 120.3, 118.6, 108.6, 42.8, 31.1, 20.5, 13.8.

N-Decylcarbazole (Table 2, entry 3) [3]. Oil; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.14$ (d, J = 10 Hz, 2H), 7.50–7.42 (q, J = 15 Hz, 4H), 7.26 (t, J = 15 Hz, 2H), 4.31 (t, J = 10.0 Hz, 2H), 1.89 (t, J = 10.0 Hz, 2H), 1.28 (s, 14H), 0.93 (t, J = 5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 140.3$, 125.4, 122.7, 120.2, 118.6, 108.5, 42.9, 29.4, 29.4, 29.3, 29.2, 28.8, 27.2, 22.5, 14.0.

N-Allylcarbazole (Table 2, entry 4) [20a]. White solid, mp 55°C (Lit. mp 55–56°C); ¹H NMR (500 MHz, CDCl₃) : δ = 8.07 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.0 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.20 (s, 2H), 5.94–5.89 (m, 1H), 5.11–5.09 (m, 1H), 4.99–4.96 (m, 1H), 4.81–4.80 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ = 140.3, 132.2, 125.6, 122.9, 120.3, 119.0, 116.7, 108.7, 45.1.

2-(Carbazol-9-yl)ethanol (Table 2, entry 5) [20b]. White solid, mp 78°C; ¹H NMR (300 MHz, CDCl₃): δ = 8.10 (d, J = 15.0 Hz, 2H), 7.47 (t, J = 5.0 Hz, 4H), 7.26–7.23 (q, J = 5.0 Hz, 2H), 4.46 (t, J = 7.5 Hz, 2H), 4.03 (t, J = 10.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ = 140.6, 125.8, 122.9, 120.3, 119.1, 108.7, 61.4, 45.4.

N-Benzylcarbazole (Table 2, entry 6) [3]. White solid, mp 117–118°C (Lit. mp 118-119°C); ¹H NMR (500 MHz, CDCl₃) : $\delta = 8.11$ (d, J = 8.0 Hz, 2H), 7.39 (s, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.22–7.20 (m, 5H), 7.09 (d, J = 6.5 Hz, 2H), 5.45 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) $\delta = 140.6$, 137.1, 128.7, 127.4, 126.3, 125.8, 122.5, 120.3, 119.1, 108.8, 46.5.

N-(*4*-*Bromobutyl*) *carbazole* (*Table 2, entry 7*) [*20c*]. White solid, mp 198–199°C; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.07-8.05$ (m, 2H), 7.43–7.33 (m, 2H), 7.22–7.18 (m, 4H), 4.25 (t, *J*=7.0 Hz, 2H), 3.29 (t, *J*=6.5 Hz, 2H), 2.00–1.96 (m, 2H), 1.87–1.82 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 140.2$, 125.6, 122.8, 120.3, 118.9, 108.5, 42.6, 33.0, 30.1, 27.5.

1,4-Di(*carbazol-9-yl*)*butane* (*Table 2, entry 8*) [20d]. White solid, mp 189°C; ¹H NMR (400 MHz, CDCl₃): δ = 8.07 (d, *J* = 7.00 Hz, 4H), 7.41 (t, *J* = 7.5 Hz, 4H), 7.24–7.19 (m, 8H), 4.14 (s, 4H), 1.90 (s, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ = 140.2, 125.6, 122.8, 120.3, 118.8, 108.5, 42.6, 26.7.

1,3-Di(carbazol-9-yl)propane (Table 2, entry 9) [20d]. White solid, mp 181°C; ¹H NMR (300 MHz, CDCl₃): $\delta = 8.07$ (d, J = 13 Hz, 4H), 7.38–7.33 (m, 4H), 7.22–7.12 (s, 8H), 4.29–4.24(t, J = 12 Hz, 4H), 2.37–2.27(t, J = 12 Hz, 4H); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 140.0$, 125.7, 122.9, 120.4, 119.0, 108.3, 40.4, 27.7.

N-Ethylindole (Table 3, entry 1) [21]. Oil; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.17-8.15$ (m, 1H), 7.73–7.70 (m, 3H), 7.43–7.42 (m, 1H), 6.98–6.97 (m, 1H), 4.40 (q, J = 7.5 Hz, 2H), 1.75 (J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 135.5$, 128.5, 126.7, 121.0, 120.7, 118.9, 109.0, 100.7, 40.4, 15.0.

N-Butylindole (Table 3, entry 2) [21]. Oil; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.22$ (d, J = 2.5 Hz, 1H), 7.85–7.67 (m, 3H), 7.47 (d, J = 3 Hz, 1H), 7.04 (d, J = 2 Hz, 1H), 4.41 (t, J = 7.1 Hz, 2H), 2.23–2.09 (m, 2H), 1.80–1.65 (m, 2H), 1.42 (t, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 135.7$, 128.4, 127.4, 121.0, 120.6, 118.9, 109.1, 100.5, 45.5, 31.9, 19.8, 13.4.

N-Decylindole (Table 3, entry 3). Oil; ¹H NMR (500 MHz, CDCl₃): δ = 7.98–7.97 (q, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.53 (t, *J* = 7 Hz, 1H), 7.46–7.44 (m, 1H), 7.33–7.32 (q, 1H), 6.82–6.81 (q, 1H), 4.32–4.28 (m, 2H), 2.08 (d, *J* = 6 Hz, 2H),1.6 (d, *J* = 5.5 Hz, 14H), 1.28–1.24 (m, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 135.8, 128.2, 127.5, 121.1, 120.8, 119.0, 109.2, 100.7, 46.1, 34.2, 32.2, 30.1, 29.4, 29.2, 29.1, 26.9, 23.0, 14.0; *Anal.* Calcd for C₁₈H₂₇N: C, 83.99; H, 10.57; N, 5.44. Found: C, 83.71; H, 10.60; N, 5.31.

N-*Benzylindole (Table 3, entry 4) [21].* Colorless solid, mp 42°C (Lit. mp 41–42°C); ¹H NMR (500 MHz, CDCl₃): δ = 7.64 (d, *J* = 7.8 Hz, 1H), 7.37–7.21 (m, 4H), 7.12–6.80 (m, 5H), 6.53 (d, *J* = 2.8 Hz, 1H), 5.24 (s, 2H); ¹³C NMR (125 MHz, CDCl₃): δ = 137.4, 136.2, 128.6, 128.1, 127.5, 126.7, 121.6, 120.9, 119.4, 109.6, 101.6, 49.9.

N-Allylindole (Table 3, entry 5) [10]. Oil; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.15$ (d, J = 7.5 Hz, 1H), 7.73–7.69 (m, 3H), 7.44 (t, J = 1.5 Hz, 1H), 7.00 (s, 1H), 6.32 (t, J = 6.5 Hz, 1H), 5.57 (d, J = 10.5 Hz, 1H), 5.47 (s, 1H), 4.97–4.93 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 135.9$, 133.3, 128.5, 127.6, 121.3, 120.7, 119.2, 116.7, 109.4, 101.1, 48.3.

1,4-Di(indol-1-yl)butane (Table 3, entry 6). White solid; mp 91–92°C; ¹H NMR (500 MHz, CDCl₃): δ =7.62 (d, J=10 Hz, 2H), 7.24 (d, J=10 Hz, 2H), 7.18 (t, J=5 Hz, 2H), 7.09 (d, J=5 Hz, 2H), 6.46 (s, 1H), 4.00 (t, J=5 Hz, 4H), 1.77 (t, J=5 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃): δ =135.8, 128.5, 127.5, 121.4, 121.0, 119.3, 109.2, 101.2, 45.8, 27.6; *Anal.* Calcd for C₂₀H₂₀N₂: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.41; H, 7.14; N, 9.59.

N-Ethylphenothiazine (Table 4, entry 1) [20a]. Light green crystal, mp 100–101°C (Lit. mp 102.5–103°C); ¹H NMR (500 MHz, CDCl₃): δ = 7.15–7.10(m, 4H), 6.91–6.83 (m, 4H), 3.93–3.86 (q, *J* = 10 Hz, 2H), 1.39 (t, *J* = 10 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 144.9, 127.3, 127.1, 124.4, 122.2, 115.0, 41.6, 12.9.

N-Butylphenothiazine(Table 4, entry 2) [22b]. Oil; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.22-7.17$ (m, 4H), 6.92 (t, J = 15 Hz, 4H), 3.88 (t, J = 10 Hz, 2H), 1.83 (t, J = 10 Hz, 2H), 1.54–1.46 (m, 2H), 0.99 (t, J = 10 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 145.2,127.2, 127.0, 124.8, 122.1, 115.3, 46.9, 28.9, 20.0, 13.7.$

N-Decylphenothiazine(Table 4, entry 3) [22c]. Oil; ¹H NMR (500 MHz, CDCl₃): δ = 7.13(d, J = 15 Hz, 4H), 6.88 (t, J = 15 Hz, 4H), 3.84 (t, J = 10 Hz, 2H), 1.89–1.79 (m, 2H), 1.44–1.29 (m, 14H), 0.90 (t, J = 10 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 145.2, 127.3, 127.0, 124.8, 122.2, 115.3, 47.3, 31.8, 29.4, 29.4, 29.4, 29.2, 28.7, 28.1, 22.6, 14.0.

N-Benzylphenothiazine (Table 4, entry 4) [22a]. White solid, mp 90–91°C (Lit. mp 90.0–90.5°C); ¹H NMR (500 MHz, CDCl₃): δ = 7.40–7.30(m, 9H), 7.12–6.85 (t, 4H), 5.10 (s, 2H); ¹³C NMR (125 MHz, CDCl₃): δ = 144.3, 141.5, 128.9, 128.3, 127.7, 127.1, 126.8, 126.4, 122.4, 115.3, 65.1.

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N-Isobutylphenothiazine (Table 4, entry 5). White solid, mp 123–125°C; ¹H NMR (500 MHz, CDCl₃): δ = 7.26–7.13(m, 4H), 6.93–6.86 (m, 4H), 3.73–3.64 (m, 2H), 2.23–2.18 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 145.8, 127.5, 127.1, 125.8, 122.3, 115.9, 55.1, 25.4, 20.1; *Anal.* Calcd for C₁₆H₁₇NS: C, 75.25; H, 6.71; N, 5.48. Found: C, 75.31; H, 6.64; N, 5.71.

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