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Indole 3-alkylation/vinylation under catalysis of the guanidinium ionic liquids

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ABSTRACT

Two ionic liquids, *N*,*N*,*N*,*N*-tetramethylguanidinium trifluoroacetate (TMGT) and the unprecedented *N*,*N*,*N*,*N*-tetramethylguanidinium triflate ($TMGT_f$), were used as catalyst solvents in condensations between indoles and arylaldehydes or 1,3-diketones providing a simple and efficient method for synthesis of bis(3-indolyl)methanes or casually 3-alkenylindoles due to stereoelectronic concerns of reactants. The ionic liquids are easily separated and reused for several times.

1. Introduction

For medicinal chemists indole is a privileged heterocyclic template, which commonly bestows diverse pharmaceutical properties on a variety of natural[1,2] and synthetic derivatives.[3] Indoles are quite ubiquitous in the plants of both marine and terrestrial domain. Among them, bis(indolyl)alkanes (BIAs) constitute an old but important class of bioactive metabolites.[4,5] For instance, bis(indolyl)-methanes are the most active cruciferous ingredients responsible for promoting beneficial estrogen metabolism in women and men,[6] meanwhile progressively are finding useful applications as breast cancer preventatives. Vanderlaag et al.[7] and Safe et al.[8] reported that 1,1-bis(3-indolyl)methanes and their ring-substituted 5,5′-dibromo derivatives induce cell death in MCF-7 and MDA-MB-231 breast cancer cells by overlapping and different pathways. In addition they are used as tranquilizers due to affecting the central nervous system and represent a novel class of uncharged mitochondrial poisons, which inhibit breast cancer cell and tumor growth. Because of these significant features there has been a great deal of interest in the synthesis of this class of compounds and consequently numerous approaches for their synthesis have been created.[9–11] The main synthetic avenue and direct method for preparation of BIAs is based on the three-component condensation of two molecules of indoles with one molecule of aldehydes or ketones in the presence of a Brønsted or Lewis acid. Three-component condensations of indoles with carbonyl compounds are slow processes by themselves. Therefore, several catalysts and reagents such as P_2O_5/SiO_2,[12] H_2NSO_3H,[13] $GaCl_3$,[14] zeolite,[15] zeokrab-225,[16] polyindole salts,[17] iodine,[18,19] montmorillonite K10,[20] CAN,[21,22] have been devised to facilitate this reaction. However despite their own merit, in some cases, Lewis acids form stable complexes or even decompose with the ligands present in reaction media, so they may need to be used in excess quantities. Some catalysts are expensive and some others suffer from the formation of by-products, long reaction time, and corrosion as well as waste acid pollution problems. Though many developments have been made to supersede the drawbacks,[23,24] there is still scope for development of mild reaction conditions using stable and reusable catalysts.

As part of ongoing studies directed toward the use of ionic liquids as catalysts and/or solvents in synthesis of organic compounds, we report herein the benefits of two Brønsted acid–base ionic liquids as efficient and recyclable catalyst solvents in the synthesis of BIAs. Ionic liquids are liquid electrolytes composed of bulky organic cations, which deserved to fill the gape of polarity between molecular liquids and the molten metal salts. The unique nature of ILs allows almost all kinds of interactions between the solutes and the ions to be established, so have an ability to dissolve both organic and inorganic materials. They can also stabilize the polar transition states thereby properly catalyze the potent reactions. Moreover, their entirely ionic structures rise to very peculiar properties,[25,26] such as negligible vapor, nonflammability, no miscibility with nonpolar solvents, and reasonable thermal and chemical stability. Another feature of ILs is their ability to be reused many times.

In following, a clean and efficient method for synthesis of bis(3-indolyl)alkanes via electrophilic substitution reaction of

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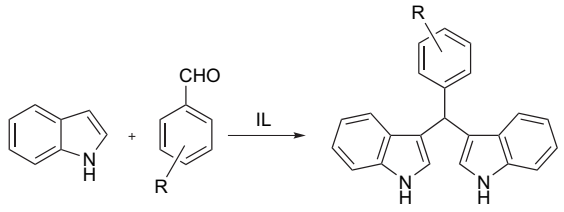
Table 1
Optimization of reaction conditions



1a **2** **3**

Entry	R	Ionic liquid	Time	Yield (%) of product **3**
1[a]	H	[BMIM]BF_4	12 h	Trace
2[b]	H	[BMIM]BF_4	4 h	Trace
3[a]	*p*-OMe	[BMIM]BF_4	12 h	Trace
4[b]	*p*-OMe	[BMIM]BF_4	4 h	Trace
5[a]	H	$TMGT_f$	12 h	Trace
6[a]	*p*-OMe	$TMGT_f$	12 h	Trace
7[a]	H	TMGT	15 min	93
8[a]	*p*-OMe	TMGT	15 min	90
9[b]	H	$TMGT_f$	90 min	92
10[b]	*p*-OMe	$TMGT_f$	120 min	88

[a] The reactions were carried out by stirring a mixture of indole (2 mmol) and aldehyde (1 mmol) in 1 mL of the ionic liquid at room temperature.
[b] The reaction mixture was sealed and heated at 100 °C.

indoles with some aldehydes or 1,3-diketones in the presence of *N*,*N*,*N*,*N*-tetramethylguanidinium triflate ($TMGT_f$) or *N*,*N*,*N*,*N*-tetramethylguanidinium trifluoroacetate (TMGT), as ionic liquid catalysts, is described.

2. Result and discussion

In addition to the aforementioned difficulties encountered in using some Brønsted or Lewis acids for catalyzing the synthesis of BIAs, many of these catalysts are not so effective as to catalyze the reaction of indoles with ketones or electron-deficient aromatic aldehydes. Notably, the neutral ionic liquid, [BMIM]BF_4, in the absence of any extra catalysts cannot catalyze this reaction.[24] In this context our attention turned to the use of mildly basic guanidinium ionic liquids, so two guanidinium salts, *N*,*N*,*N*,*N*-tetramethylguanidinium trifluoroacetate (TMGT)[27] and *N*,*N*,*N*,*N*-tetramethylguanidinium triflate ($TMGT_f$), were selected as possible ionic liquid catalysts for trials of these reactions. Results of our preliminary experiments on effecting two model reactions, between indole and benzaldehyde or *p*-methoxybenzaldehyde (Table 1), in the presence of three ionic liquids have shown the efficiency of guanidinium ionic liquids and supremacy of TMGT. Also to optimize the reaction conditions, we performed the model reactions using different quantities of reactants and TMGT or $TMGT_f$. The best results were obtained with 2:1 mmol ratios of indoles and carbonyl compounds in the presence of 1 mL of the ionic liquid at room temperature for TMGT and 100 °C for $TMGT_f$.

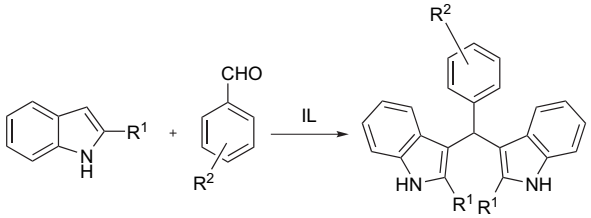
We therefore set out a method comprising the room-temperature reaction of a 2:1 mixture of indole **1** and aldehyde **2** without using any solvent or additional catalyst in TMGT and thereby bis-(indolyl)methanes **3a–j** were obtained in fairly high yields (Table 2). It is noteworthy that both electron-rich (Table 2, entry 2) as well as electron-deficient aldehydes (Table 2, entries 4 and 6) reacted effectively with indoles under these reaction conditions. It is also important to note that in the absence of ILs only trace reaction yields were observed, even at 100 °C and with longer reaction times.

The condensation of indoles with carbonyl compounds is better rationalized by consecutive nucleophilic addition of the indole onto the carbonyl group and dehydration of the addition product to give the azafulvaline intermediate **5**. The reaction then is followed by nucleophilic addition of the second indole molecule onto the azafulvaline intermediate **5**, (Scheme 1).

Similarly, 1,3-dicarbonyl compounds such as acetylacetone and dimedone reacted with indole to produce the corresponding geminal bis(indolyl)ketones in fairly high yields (Table 3).

Interestingly, no products resulting from the addition of indoles on both carbonyl groups are isolated. This convergence can be explained on the basis of the above proposed mechanism and concerning that the azafulvaline moiety, **5**, is more reactive toward nucleophilic additions relative to the other carbonyl group existing in the same intermediate. In the case of reaction between indole derivatives and dibenzoylmethane, **4b**, the sole product is 1,3-diphenyl-3-(3-indolyl)-2-propen-1-one, **6b–c**. This observation can be rationalized by the steric prevented addition of the second indole molecule onto the azafulvaline intermediate. The reactive azafulvaline

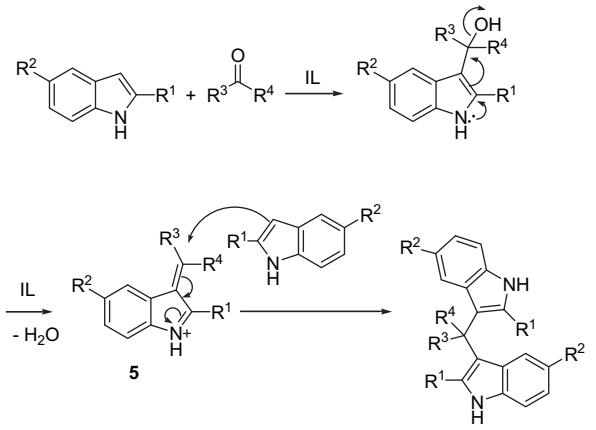
Table 2
Synthesis of bis(indolyl)methanes from indoles and aldehydes in the ionic liquids, TMGT, and $TMGT_f$



1a **2 (a-h)** **3**

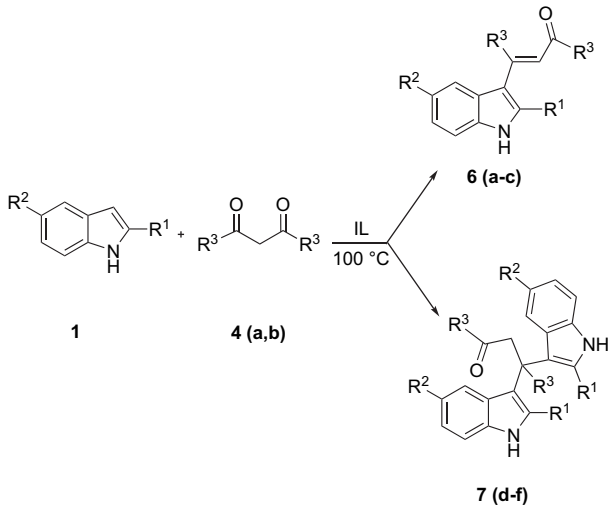
Entry	R_1	Aldehyde	Product[c]	Time (% yield)		Mp (°C)	
				TMGT[a]	$TMGT_f$[b]	Found	Reported[c]
1	H	**2a** (R^2=H)	**3a**	15 min (93)	1.5 h (93)	142–144	140–142
2	H	**2b** (R^2=*p*-OMe)	**3b**	15 min (85)	2 h (84)	187–189	186–188
3	H	**2c** (R^2=*p*-Me)	**3c**	15 min (90)	2 h (89)	96–97	95–97
4	H	**2d** (R^2=*p*-NO_2)	**3d**	10 min (92)	1 h (91)	218–220	217–219
5	H	**2e** (R^2=*p*-Cl)	**3e**	15 min (87)	2 h (84)	76–77	78–80
6	H	**2f** (R^2=*m*-NO_2)	**3f**	10 min (88)	1.5 h (85)	221–223	220–222
7	Me	**2g** (R^2=H)	**3g**	5 min (92)	1 h (91)	244–246	244–246
8	Me	**2h** (R^2=*p*-Me)	**3h**	10 min (90)	1.5 h (90)	174–176	175–177
9	H	Cinnamaldehyde	**3i**	15 min (93)	2 h (85)	98–100	100–102

[a] The reactions were carried out by stirring a mixture of indole (2 mmol) and aldehyde (1 mmol) in 1 mL of the ionic liquid at room temperature.
[b] The reaction mixture was sealed and heated at 100 °C.
[c] See Ref. 12.



Scheme 1. A plausible mechanism for the reaction.

Table 3
Synthesis of bis(indolyl)ketones from indoles and 1,3-dicarbonyl compounds in the ionic liquids



Entry	Indole		1,3-Dicarbonyl comp.	Product	Time (% yield)		Mp (°C)	
	R^1	R^2			TMGT[b]	$TMGT_f$[c]	Found	Reported
1	H	H	**4a** (R^3=Me)	**7d**[a]	35 min (95)	4 h (93)	223–225	226–228[a]
2	H	Br	**4a** (R^3=Me)	**7e**	1 h (92)	4 h (92)	220–222	—
3	H	Br	Dimedone	**7f**	25 min (96)	5 h (89)	214–216	—
4	Me	H	**4a** (R^3=Me)	**6a**	20 min (98)	3.5 h (90)	109–110	108–110[d]
5	Me	H	**4b** (R^3=Ph)	**6b**	25 min (93)	5 h (88)	185–187	—
6	H	Br	**4b** (R^3=Ph)	**6c**	1 h (89)	5 h (86)	219–220	—

[a] See Ref. 12.
[b] At room temperature.
[c] The reaction mixture was sealed and heated at 100 °C.
[d] See Ref. 28.

intermediate thus tautomerizes to the product 1,3-diphenyl-3-(3-indolyl)-2-propen-1-one in which the intact carbonyl group can gain more stabilization by conjugation and thus become unreactive toward nucleophilic addition of the second indole molecule. The relatively hindered reaction of 2-methylindole with 2,4-pentandione likewise resulted in the formation of enone **6a**.

3. Experimental section

3.1. General

All of the solvents and reagents were purchased from Fluka or Merck chemical companies. Melting points were measured on a electrothermal apparatus and are uncorrected. Elemental analysis for C, H, and N were performed using a Foss Heraus CHN-O-rapid analyzer. IR spectra were obtained in KBr wafers on Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Brucker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. Chemical shifts of ^{1}H and ^{13}C NMR spectra were expressed in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV.

3.2. Procedure for preparation of *N,N,N,N*-tetramethylguanidinium triflate ($TMGT_f$)

To a stirred mixture of *N,N,N,N*-tetramethylguanidine (0.56 g, 5 mmol) in anhydrous diethylether (10 mL) at 0 °C (ice bath) was added dropwise a solution of (0.75 g, 5 mmol) trifluoromethanesulfonic acid in anhydrous diethylether (2 mL). The reaction mixture was stirred for 30 min, and then the solvent was removed under vacuum to obtain the guanidinium salt as pale yellow oil.

3.3. General procedure for preparation of bis(3-indolyl) methanes

A mixture of indole (2 mmol) and an aldehyde or a 1,3-dicarbonyl compound (1 mmol) was added to a vial containing a magnetic stirring bar and the ionic liquid (TMGT or $TMGT_f$, 1 mL). The reaction mixtures were sealed and heated at 100 °C in an oil bath for the time specified in Tables 2 and 3. It is noticeable that the reaction of indoles and aldehydes in TMGT was carried out by stirring a mixture of the indole (2 mmol) and the aldehyde (1 mmol) in 1 mL of TMGT at room temperature. After the appropriate time (Tables 2 and 3) when the reactions were complete, as indicated by TLC, the product was extracted with 2×15 mL of cold diethylether. The ethereal solution was evaporated at reduced pressure and the remaining solid was recrystallized from ethanol (95.5%) to afford the pure products. After extraction of products, the volatiles of the ionic liquid residue were removed in vacuum and the remaining ionic liquid layer was collected and reused for the next run. All the known products have spectral and physical data consistent with those reported in literatures as well as the samples prepared from previously reported methods. The new products were characterized by their IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data as well as elemental analysis.

3.4. 3-((1*H*-Indol-3-yl)(phenyl)methyl)-1*H*-indole (3a)

Pink solid (0.30 g, 93%), mp 142–144 °C, lit.[12] mp 140–142 °C; δ_H (500.1 MHz, $CDCl_3$) 7.80 (2H, br s, two NH), 7.28–7.22 (4H, m), 7.19–7.15 (4H, m), 7.10 (1H, t, *J* 6.9 Hz), 7.02 (2H, t, *J* 7.7 Hz), 6.85 (2H, t, *J* 7.6 Hz), 6.60 (1H, s), 6.57 (1H, s), 5.78 (1H, s, PhCH).

3.5. 3-((1*H*-Indol-3-yl)(4-methoxyphenyl)-methyl)-1*H*-indole (3b)

Brown solid (0.30 g, 85%), mp 187–189 °C, lit.[12] mp 186–188 °C; δ_H (500.1 MHz, $CDCl_3$) 7.9 (2H, br s, two NH), 7.42 (2H, d, *J* 8.0 Hz), 7.39 (2H, d, *J* 8.1 Hz), 7.29 (1H, d, *J* 6.9 Hz, Ar), 7.20 (2H, t, *J* 7.6 Hz), 7.04 (2H, t, *J* 7.5 Hz), 6.86 (2H, d, *J* 6.9 Hz, Ar), 6.70 (2H, s, two 2-H of indoles), 5.88 (1H, s, ArCH), 3.82 (3H, s, OCH_3).

3.6. 3-((1*H*-Indol-3-yl)(4-methylphenyl)methyl)-1*H*-indole (3c)

Pink solid (0.30 g, 90%), mp 96–97 °C, lit.[12] mp 95–97 °C; δ_H (500.1 MHz, DMSO-d_6) 10.91 (2H, br s, two NH), 8.15 (2H, d, *J* 8.7 Hz, Ar), 7.60 (2H, d, *J* 8.7 Hz, Ar), 7.36 (2H, d, *J* 8.1 Hz), 7.28 (2H, d,

J 7.9 Hz), 7.05 (2H, t, *J* 7.6 Hz), 6.90 (2H, s, two 2-H of indoles), 6.88 (2H, t, *J* 7.1 Hz), 6.02 (1H, s, ArCH), 2.50 (3H, s, CH_3).

3.7. 3-((1*H*-Indol-3-yl)(4-nitrophenyl)methyl)-1*H*-indole (3d)

Yellow needles (0.34 g, 92%), mp 218–220 °C, lit.[12] mp 217–219 °C; δ_H (500.1 MHz, DMSO-d_6) 10.92 (2H, br s, two NH), 8.15 (2H, d, *J* 8.7 Hz, Ar), 7.61 (2H, d, *J* 8.7 Hz, Ar), 7.37 (2H, d, *J* 8.1 Hz), 7.29 (2H, d, *J* 7.9 Hz), 7.05 (2H, t, *J* 7.4 Hz), 6.90 (2H, s, two 2-H of indoles), 6.88 (2H, t, 7.5 Hz), 6.03 (1H, s, ArCH).

3.8. 3-((1*H*-Indol-3-yl)(4-chlorophenyl)methyl)-1*H*-indole (3e)

Pink solid (0.31 g, 87%), mp 76–77 °C, lit.[12] mp 78–80 °C; δ_H (500.1 MHz, $CDCl_3$) 7.96 (2H, br s, two NH), 7.40 (4H, d, *J* 8.5 Hz), 7.32–7.27 (4H, m, Ar), 7.23 (2H, t, *J* 8.1), 7.05 (2H, t, *J* 7.8 Hz), 6.69 and 6.68 (2H, 2s, two 2-H of indoles), 5.90 (1H, s, ArCH).

3.9. 3-((1*H*-Indol-3-yl)(3-nitrophenyl)methyl)-1*H*-indole (3f)

Yellow solid (0.32 g, 88%), mp 221–223 °C, lit.[12] mp 220–222 °C; δ_H (500.1 MHz, $CDCl_3$) 8.25 (1H, t, *J* 1.7 Hz, Ar 2′-H), 8.12 (1H, dd, *J* 8.1 and 1.3 Hz, Ar 4′-H), 8.04 (2H, br s, two NH), 7.73 (1H, d, *J* 7.7 Hz, Ar 6′-H), 7.48 (1H, t, *J* 7.9 Hz, Ar 5′-H), 7.42 (2H, d, *J* 8.2 Hz), 7.39 (2H, d, *J* 7.9 Hz), 7.23 (2H, t, *J* 7.6 Hz), 7.06 (2H, t, *J* 7.9 Hz), 6.73 (2H, br s, two 2-H of indoles), 6.04 (1H, s, ArCH).

3.10. 2-Methyl-3-((2-methyl-1*H*-indol-3-yl)(phenyl)methyl)-1*H*-indole (3g)

Pink solid (0.32 g, 92%), mp 244–246 °C, lit.[12] mp 244–246; δ_H (500.1 MHz, $CDCl_3$) 7.75 (2H, br s, two NH), 7.32–7.23 (7H, m), 7.07 (2H, t, *J* 7.6 Hz), 7.01 (2H, d, *J* 8.0 Hz), 6.89 (2H, t, *J* 7.5 Hz), 6.04 (1H, s, PhCH), 2.10 (6H, s, $2CH_3$).

3.11. 2-Methyl-3-((2-methyl-1*H*-indol-3-yl)-(4-methylphenyl)methyl)-1*H*-indole (3h)

Pink solid (0.33 g, 90%), mp 174–176 °C, lit.[12] mp 175–177 °C; δ_H (500.1 MHz, $CDCl_3$) 7.70 (2H, br s, two NH), 7.26 (2H, d, *J* 8.0 Hz), 7.20 (2H, d, *J* 8.0 Hz), 7.09 (2H, d, *J* 7.3 Hz), 7.07 (2H, t, *J* 7.9 Hz), 7.04 (2H, d, *J* 8.0 Hz), 6.90 (2H, t, *J* 7.5 Hz), 6.00 (1H, s, ArCH), 2.38 (3H, s, Ar 4′-CH_3), 2.09 (6H, s, indoles 2-CH_3).

3.12. *E*-3-(1-(1*H*-Indol-3-yl)-3-phenylallyl)-1*H*-indole (3i)

Pale yellow solid (0.32 g, 93%), mp 98–100 °C, lit.[12] mp 100–102 °C; δ_H (500.1 MHz, DMSO-d_6) 10.83 (2H, br s, two NH), 7.50 (2H, d, 7.9 Hz), 7.40 (2H, t, *J* 7.6 Hz), 7.33 (2H, d, *J* 8.1 Hz), 7.29–7.24 (3H, m), 7.18 (1H, t, 7.4 Hz), 7.14 and 7.13 (2H, 2s, two 2-H of indoles), 7.02 (2H, t, *J* 7.2 Hz), 6.89 (2H, t, 7.5 Hz), 6.55 (1H, d, *J* 15.4 Hz), 5.35 (1H, d, *J* 7.0 Hz).

3.13. 4-(2-Methyl-1*H*-3-indolyl)-3-penten-2-one (6a)

Brown solid (0.21 g, 98%), mp 109–110 °C, lit.[28] mp 108–110 °C; δ_H (500.1 MHz, $CDCl_3$) 8.68 (1H, br s, NH), 7.62–7.21 (4H, m), 6.28 (1H, s, 3-H), 2.58 (3H, s, CH_3), 2.49 (3H, s, CH_3), 2.29 (3H, s, CH_3).

3.14. 3-(2-Methyl-1*H*-indol-3-yl)-1,3-diphenyl-prop-2-en-1-one (6b)

Orange solid (0.31 g, 93%), mp 185–187 °C; [Found C, 85.5; H, 5.7; N, 4.0. $C_{24}H_{19}NO$ requires C, 85.43; H, 5.68; N, 4.15%]; ν_{max} (KBr) 3250, 1620, 1550, 1460, 1240, 770 cm^{-1}; δ_H (500.1 MHz, $CDCl_3$) 9.92 (1H, s), 7.57 (2H, d, *J* 7.5 Hz), 7.29 (2H, d, *J* 7.0 Hz), 7.10–7.20 (4H, m), 6.97–7.01 (3H, m), 6.85 (1H, s), 6.78 (1H, t), 6.64 (2H, m), 1.93 (3H, s); δ_C (125.8 MHz, $CDCl_3$) 193.2, 149.8, 1414.9, 139.2, 137.5, 135.9, 131.9, 129.6, 128.9, 128.7, 128.4, 128.2, 128.0, 123.4, 121.1, 119.8, 119.6, 112.0, 110.8, 13.4; *m*/*z* (EI, 70 eV) 337 (30, M^+), 325 (29), 324 (100), 315 (60), 253 (19), 156 (67).

3.15. 3-(5-Bromo-1*H*-indol-3-yl)-1,3-diphenylprop-2-en-1-one (6c)

Orange solid (0.37 g, 89%), mp 219–220 °C; [Found C, 68.7; H, 4.1; N, 3.4. $C_{23}H_{16}BrNO$ requires C, 68.67; H, 4.01; N, 3.48%]; ν_{max} (KBr) 3402, 2905, 1540, 1420, 1100, 862, 800 cm^{-1}; δ_H (500.1 MHz, DMSO) 11.9 (1H, s), 7.90 (2H, d, *J* 7.3 Hz), 7.55 (1H, t, *J* 7.3 Hz), 7.52 (1H, s), 7.43–7.48 (3H, m), 7.32–7.36 (4H, m), 7.27 (1H, d, *J* 8.2 Hz), 7.26 (1H, s), 7.22 (2H, d, *J* 6.7 Hz); δ_C (125.8 MHz, DMSO) 191.3, 151.0, 140.9, 139.9, 136.9, 133.1, 131.6, 130.0, 129.4, 129.0, 128.8, 127.9, 125.5, 123.2, 119.0, 117.5, 115.2, 114.0; *m*/*z* (EI, 70 eV) 405 (23, ^{81}Br ^{81}Br, MH^+), 403 (98, ^{81}Br ^{79}Br, MH^+), 401 (96, ^{79}Br ^{79}Br, MH^+), 326 (51), 324 (52), 293 (37), 245 (65), 217 (100), 189 (60%).

3.16. 4,4-Bis(1*H*-indol-3-yl)pentan-2-one (7d)

Colorless solid (0.30 g, 95%), mp 223–225 °C, lit.[12] mp 226–228; [Found C, 79.6; H, 6.3; N, 8.9. $C_{21}H_{20}N_2O$ requires C, 79.72; H, 6.37; N, 8.85%]; ν_{max} (KBr) 3421, 3259, 2920, 1691, 1450, 1340, 1014, 750 cm^{-1}; δ_H (500.1 MHz, $CDCl_3$) 8.04 (2H, br s, two NH), 7.40 (2H, d, *J* 8.0 Hz), 7.37 (2H, d, *J* 8.1 Hz), 7.11–7.14 (4H, m, overlap of one triplet and two singlets), 6.92 (2H, t, *J* 7.6 Hz), 3.56 (2H, s, CH_2), 2.03 (3H, s, Me), 1.58 (3H, s, Me); δ_C (125.8 MHz, $CDCl_3$) 209.8 (C=O), 137.4 (3 aromatic C), 126.4, 123.4, 122.1 (5CH), 121.7, 121.4, 119.5, 111.6, 53.7 (C-4), 38.3, 32.4, 27.7; *m*/*z* (EI, 70 eV) 316 (95, M^+), 260 (75), 259 (100), 142 (50), 115 (34%).

3.17. 4,4-Bis(5-bromo-1*H*-indol-3-yl)pentan-2-one (7e)

White solid (0.44 g, 92%), mp 220–222 °C; [Found C, 53.1; H, 3.9; N, 5.9. $C_{21}H_{18}Br_2N_2O$ requires C, 53.19; H, 3.83; N, 5.91%]; ν_{max} (KBr) 3350, 2900, 1680, 1450, 1115, 880, 800 cm^{-1}; δ_H (500.1 MHz, DMSO) 11.13 (2H, s, 2 NH), 7.43 (2H, d, *J* 2 Hz, 4′-H), 7.30 (2H, d, *J* 8.6 Hz, 7′-H), 7.17 (2H, d, *J* 1.1 Hz, 2′-H), 7.05 (2H, dd, *J* 8.6, 1.7 Hz, 6′-H), 3.39 (2H, s, CH_2), 1.84 (3H, s, Me), 1.59 (3H, s, Me); δ_C (125.8 MHz, DMSO) 208.4 (C=O), 136.6 (4 aromatic C), 128.2, 124.3, 124.0 (4CH), 122.6, 122.0, 114.4, 111.4, 53.5 (C-4), 37.4, 32.6, 27.8; *m*/*z* (EI, 70 eV) 476 (15, ^{81}Br ^{81}Br, M^+), 474 (30, ^{81}Br ^{79}Br, M^+), 472 (16, ^{79}Br ^{79}Br, M^+), 419 (80), 417 (100), 415 (73), 197 (34), 183 (42%).

3.18. 3,3-Bis(5-bromo-1*H*-indol-3-yl)-5,5-dimethylcyclohexanone (7f)

White solid (0.49 g, 96%), mp 214–216 °C; [Found C, 56.1; H, 4.3; N, 5.3. $C_{24}H_{22}Br_2N_2O$ requires C, 56.05; H, 4.31; N, 5.45%]; ν_{max} (KBr) 3350, 3250, 1580, 1520, 1490, 1480, 1040, 820, 620 cm^{-1}; δ_H (500.1 MHz, DMSO) 10.59 (1H, s, NH), 8.79 (1H, s, NH), 7.83 (1H, s), 7.18 (1H, d, *J* 8.6 Hz), 7.12 (2H, br m), 7.02 (1H, d, *J* 8.6 Hz), 6.76 (1H, d, *J* 1.2 Hz), 6.30 (1H, s), 5.10 (1H, d, *J* 5.2 Hz, 2′-H), 3.24 (1H, dd, *J* 14.2 and 6.0 Hz, 2-H_B), 2.97 (1H, d, *J* 14.2 Hz, 2-H_A), 2.60 (2H, s, CH_2), 2.16 (1H, d, *J* 16 Hz, 4-H_B), 2.12 (1H, d, *J* 16 Hz, 4-H_A), 1.07 (3H, s, Me), 1.03 (3H, s, Me); δ_C (125.8 MHz, DMSO) 194.2, 153.5, 140.7, 135.6, 133.7, 132.4, 129.7, 128.8, 124.7, 124.0, 122.4, 121.8, 119.1, 114.8, 114.1, 114.0, 111.7, 50.7, 45.5, 39.8, 32.6, 32.0, 28.9, 28.5; *m*/*z* (EI, 70 eV) 516 (26, ^{81}Br ^{81}Br, M^+), 514 (51, ^{81}Br ^{79}Br, M^+), 512 (27, ^{79}Br ^{79}Br, M^+), 501 (83), 499 (100), 497 (90), 319 (45), 317 (45%).

4. Conclusion

In summary, an efficient and convenient approach for the synthesis of bis(indolyl)alkanes using guanidinium ionic liquids is introduced here. The ionic liquids can be recovered simply by biphasic separation and reused for several times without considerable decrease in yields of products. The one-pot and solvent-free achieving of products in the absence of any additional catalyst are the prominent features of this approach. Apparently the azafulvaline moiety derived from a 1,3-dicarbonyl compound is more reactive toward nucleophilic addition relative to the intact carbonyl group, present in the same intermediate, as the two indole molecules react at the same carbonyl carbon to produce the geminal bis(3-indolyl)ketones **7d**–**f**.

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