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N-Alkylation of 1*H*-indoles and 9*H*-carbazoles with alcohols

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Abstract—A comparative study of *N*-alkylation of 1*H*-indole and 9*H*-carbazole derivatives with alcohol derivatives was performed using classic Mitsunobu reaction conditions, i.e. DEAD/PPh_3, azodicarboxamide derivatives such as TMAD in the presence of PBu_3, or using phosphorane derivatives such as CMMP.

The Mitsunobu reaction is a very versatile method for the alkylation using aliphatic alcohols as electrophilic partners under mild conditions.[1] Yet applications of the Mitsunobu reaction to achieve *N*-alkylation with alcohols have been rather limited in scope. One example of *N*-alkylation using the Mitsunobu reaction was reported with indole bearing electron withdrawing groups.[2] To our knowledge no Mitsunobu reaction was reported using 9*H*-carbazole compounds. Our objective was to identify and compare experimental conditions that would allow direct *N*-alkylation of substituted 1*H*-indole and 9*H*-carbazole derivatives. The classic Mitsunobu set of reagents diethyl azodicarboxylate/triphenylphosphine (DEAD/PPh_3) was compared to the use of the *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide/tributylphosphine (TMAD/PBu_3) tandem and to the use of cyanomethylenetrimethyl phosphorane ($Me_3P{=}CH(CN)$, CMMP). Tsunoda and co-workers showed the efficiency of TMAD/PBu_3 over DEAD/PPh_3 for the preparation of secondary amines.[3] Ito and co-workers reported that phosphoranes such as CMMP were the most powerful *C*-alkylating agents for the weak acidic nucleophiles.[4] And recently Zaragosa reported that CMMP could promote *N*-alkylation of secondary amines by alcohols.[5]

Our initial experiments began by studying the Mitsunobu reaction of 5-bromo-1*H*-indole with primary alcohols such as benzyl alcohol and (±)-glycidol, and secondary alcohols such as (±)-octan-2-ol. The reaction with (±)-glycidol was attractive due to possible further functionalisation on the Mitsunobu adduct **1b**. The standard Mitsunobu conditions (DEAD/PPh_3) failed to give any expected condensation product (Table 1, entries 1–3). This result might be explained by the weak acidity of 5-bromo-1*H*-indole.[6] The use of TMAD/PBu_3 enhanced the reactivity of 5-bromo-1*H*-indole towards primary alcohols and compounds **1a** and **1b** were obtained in a poor to moderate yield. In contrast no reaction was observed with (±)-octan-2-ol under the same reaction conditions. The use of CMMP improved dramatically the reactivity of 5-bromo-1*H*-indole and excellent yields were obtained independently of the use of secondary or primary alcohols (see entries 1 and 3). However, the reaction with (±)-glycidol was found to be difficult to control: using strictly 1 equiv. of each reagent gave the Mitsunobu product **1b** in a 49% yield, while an excess of reagents and/or high temperature favour the formation of a by-product. This compound was identified to be the elimination product of the alcohol derivative which was formed from a second attack of the indole onto the epoxide **1b**.[7] It was of interest to note that the use of TMAD/PBu_3 and CMMP led to an easy work-up, preventing the tedious separation of $PPh_3{=}(O)$.

Encouraged by these results, the chemical reactivity of carbazole derivatives was evaluated under the same set of experiments. Using the classic Mitsunobu conditions (DEAD/PPh_3), 3,6-dibromo-9*H*-carbazole and 3-nitro-9*H*-carbazole, which were reported to be slightly better acids than indoles,[8] exhibited varying reactivity with benzyl alcohol, (±)-glycidol and (±)-octan-2-ol (entries 4–9). The reactivity with benzyl alcohol was significantly increased using the TMAD/PBu_3 tandem. As it was observed for the 5-bromo-1*H*-indole derivative, the reactivity of carbazole derivatives with the secondary alcohol was sluggish when using the DEAD/PPh_3 or TMAD/PBu_3 tandem (entries 8 and 9). The use of CMMP could improve significantly the reactivity of carbazoles with the secondary alcohol and afforded

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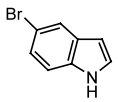
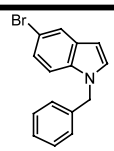
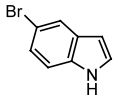
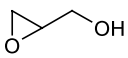
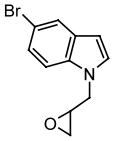
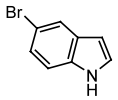
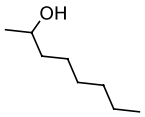
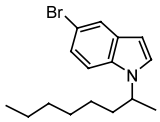
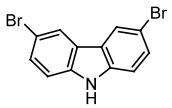
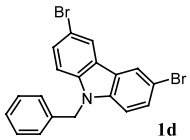
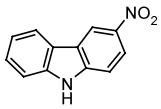
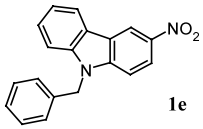
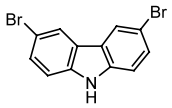
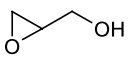
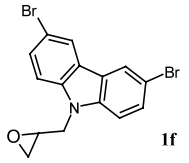
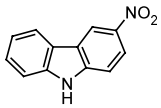
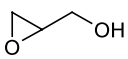
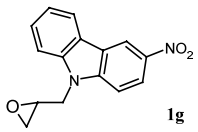
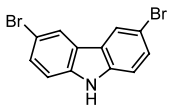
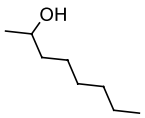
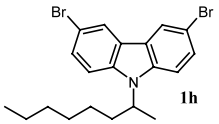
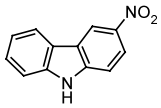
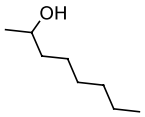
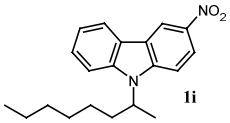
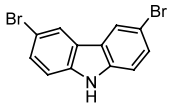
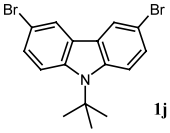
Table 1. *N*-Alkylation of 1*H*-indole and 9*H*-carbazole derivatives with alcohols

Entry	Amine	Alcohol	Product	DEAD/PPh_3[a] Yield (%)	TMAD/PBu_3[b] Yield (%)	CMMP[c] Yield (%)
1			 **1a**	0	20	88
2			 **1b**	0[d]	25[d]	49[d]
3			 **1c**	0	Traces	93
4			 **1d**	31	95	97
5			 **1e**	65	95	91
6			 **1f**	65[d]	44[d]	25[d]
7			 **1g**	95[d]	25[d]	25[d]
8			 **1h**	30	25	97
9			 **1i**	ND	15	82
10			 **1j**	ND	ND	70[e]

[a] DEAD (2 equiv.), PPh_3 (2 equiv.), alcohol (2 equiv.) and amine in THF, 40°C, 15 h.[9]

[b] TMAD (2 equiv.), PBu_3 (2 equiv.), alcohol (2 equiv.) and amine in toluene, 40°C, 15 h.[10]

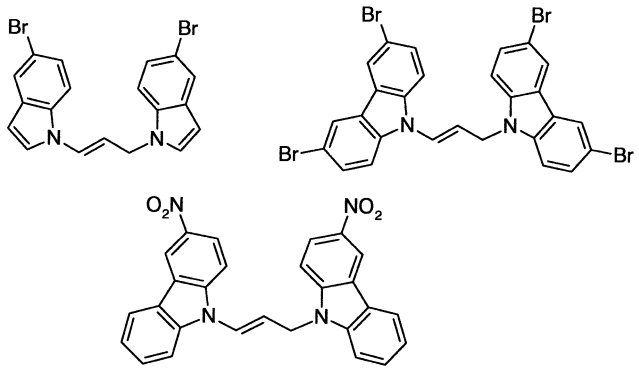
[c] CMMP (2 equiv.), alcohol (2 equiv.) and amine (1 equiv.) in toluene, 110°C, 15 h.[11]

[d] The temperature was maintained at 25°C and one equiv. of each reagent was used.

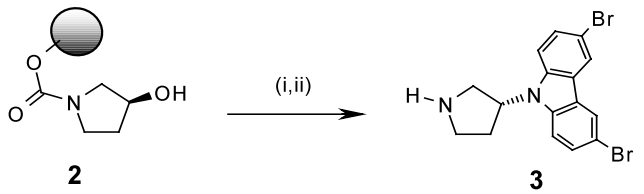
[e] A THF solution of 3,6-dibromo-9*H*-carbazole and cyanomethyl-trimethyl-phosphonium chloride was treated with *t*-BuOK at 0°C, and the reaction mixture was then stirred at 80°C for 15 h.

similar yields with benzyl alcohol compared with the TMAD/PBu_3 tandem.

To extend the scope of the use of CMMP with carbazole derivatives, the reactivity with tertiary alcohol was evaluated. Preliminary results showed that 3,6-dibromo-9*H*-carbazole could undergo *N*-alkylation with *tert*-butanol using a one-pot protocol of CMMP (entry 10) to give the product **1j** in 70% yield. The one-pot protocol of CMMP was found to be convenient and was compared to the previously described general procedure. For instance, the compounds **1a** and **1d** were obtained with similar yields performing or not the initial preparation of the phosphorane.[12] Furthermore, *N*-alkylation of 3,6-dibromo-9*H*-carbazole could be performed to a supported (*S*)-3-hydroxy-pyrrolidine derivative, as outlined in Scheme 1. *p*-Nitrophenylcarbonate Wang resin was attached to (*S*)-3-pyrrolidinol to give the resin bound compound **2**. Then the Mistusnobu coupling with 3,6-dibromo-9*H*-carbazole using the TMAD/PBu_3 tandem gave, after cleavage with TFA:CH_2Cl_2, the desired compound **3** in a 60% yield in 99.8% ee.



In conclusion we demonstrated that CMMP is the reagent of choice for the *N*-alkylation of 1*H*-indole and 9*H*-carbazole derivatives with alcohol derivatives. In addition the TMAD/PBu_3 tandem can efficiently *N*-alkylate 1*H*-indole derivatives with primary and secondary alcohols, and DEAD/PPh_3, TMAD/PBu_3 and CMMP can efficiently *N*-alkylate 9*H*-carbazole derivatives with primary and secondary alcohols. Further SPS applications and the scope of alcohols, especially tertiary alcohols, are under investigation.



Scheme 1. SPS application. (i) 3,6-Dibromo-9*H*-carbazole, TMAD, PBu_3; (ii) TFA/CH_2Cl_2 (5/1).

Acknowledgements

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References

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3. Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett*. **1994**, 539–542.
4. Tsunoda, T.; Ito, S. *Pure Appl. Chem*. **1999**, *71*, 1053–1057.
5. Zaragosa, F.; Stephensen, H. *J. Org. Chem*. **2001**, *66*, 2518–2521 and *Tetrahedron Lett*. **2000**, *41*, 1841–1844.
6. The calculated p*K*a of substituted-1*H*-indole is about 15–17 in water according to the ACD/p*K*a DB version 3.5, and 21 in DMSO according to Bordwell, F. G. *Acc. Chem. Res*. **1988**, *21*, 456–463.
7. The following by-products, which were fully characterized, were obtained for entries 2, 6 and 7, respectively.
8. Zherebtsov, I. P.; Lopatinskii, V. P. *Izv. Tomsk. Politekh. Inst*. **1970**, *163*, 12–17. [*CA* **75**, 117862x (1971)].
9. **General procedure using the classic Mitsunobu conditions**. 9-Benzyl-3,6-dibromo-9*H*-carbazole **1d**. At 25°C in a 25 mL Schlenk flask under an argon atmosphere, benzyl alcohol (0.134 g, 1.24 mmol, 0.13 mL) was added into an anhydrous THF solution (5 mL) of 3,6-dibromo-9*H*-carbazole (0.2 g, 0.62 mmol) and PPh_3 (0.325 g, 1.24 mmol). At 0°C, DEAD (0.216 g, 1.24 mmol, 0.19 mL) was added neat and the reaction mixture was stirred for 15 h at 40°C. TLC monitoring (SiO_2, petroleum ether/DCM, 48/1) showed formation of a new UV active compound (R_f=0.12). Flash chromatography (SiO_2, PE/DCM, 48/1) gave 80 mg of **1d** as a white powder in a 31% yield. Mp 155–160°C. ^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm) 8.5 (m, 2H), 7.6 (m, 4H), 7.3 (m, 3H), 7.1 (m, 2H), 5.7 (s, 2H). ^{13}C NMR: (75.5 MHz, DMSO-d_6) δ (ppm) 140.2, 138.1, 129.9, 129.6, 128.3, 127.5, 124.5, 124.0, 112.8, 112.5, 46.7. Anal. calcd for $C_{19}H_{13}Br_2N$: C, 54.97; H, 3.16; N, 3.37. Found: C, 55.21; H, 3.33; N, 3.44%. 9-Benzyl-3-nitro-9*H*-carbazole **1e**. Yield 65%. Yellow powder. Mp 120.5°C. ^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm) 9.2 (m, 1H), 8.5 (m, 1H), 8.3 (dd, J=9.2, 2.4 Hz, 1H), 7.85 (m, 1H) 7.8 (m, 1H), 7.6 (m, 1H), 7.3 (m, 6H), 5.8 (s, 2H). ^{13}C NMR: (75.5 MHz, DMSO-d_6) δ (ppm) 144.3, 142.4, 141.1, 137.8, 129.6, 128.4, 127.6, 123.2, 123.0, 122.4, 122.4, 121.7, 118.3, 111.5, 110.7, 46.9. Anal. calcd for $C_{19}H_{14}N_2O_2$ C, 75.48; H, 4.67; N, 9.27. Found: C, 75.36; H, 4.73; N, 9.27%. 3,6-Dibromo-9-oxiranylmethyl-9*H*-carbazole **1f**. Yield 65%. White solid. Mp 147.5°C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 8.1 (m, 2H), 7.6 (dd, J=8.7, 1.9 Hz, 2H), 7.3 (d, J=8.7 Hz, 2H), 4.7 (dd, J=15.8, 2.6 Hz, 1H), 4.3 (dd, J=15.8, 5.2 Hz, 1H), 3.3 (m, 1H), 2.8 (t, J=4.3 Hz, 1H), 2.5 (dd, J=4.9, 2.6 Hz, 1H). ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ (ppm) 139.9, 129.6, 123.9, 123.5, 112.9, 110.9, 50.7, 45.3, 45.1. Anal. calcd for $C_{15}H_{11}Br_2NO_2$ (*c*-hexane): C, 59.43; H,

6.54; N, 2.51. Found: C, 59.84; H, 6.55; N, 2.53%. 3-Nitro-9-oxiranylmethyl-9*H*-carbazole **3g**. Yield 95%. Yellow solid. Mp 153.5°C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 9.2 (d, $J=2.3$ Hz, 1H), 8.4 (m, 1H), 8.4 (dd, $J=9.0$, 2.2 Hz, 1H), 7.9 (d, $J=9.0$ Hz, 1H), 7.8 (m, 1H), 7.6 (m, 1H), 7.3 (t, $J=7.5$ Hz, 1H), 4.9 (dd, $J=15.8$, 3.0 Hz, 1H), 4.5 (dd, $J=15.6$, 5.8 Hz, 1H), 3.4 (m, 1H), 2.8 (t, $J=7.5$ Hz, 1H), 2.5 (dd, $J=4.9$, 2.6 Hz, 1H).

10. **General procedure using TMAD/PBu$_3$**. 9-Benzyl-3,6-dibromo-9*H*-carbazole **1d**. At 25°C in a 25 mL Schlenk flask, under an argon atmosphere, benzyl alcohol (0.134 g, 1.24 mmol, 0.13 mL) was added into a solution of 3,6-dibromo-9*H*-carbazole (0.2 g, 0.62 mmol) and PBu_3 (0.25 g, 1.24 mmol, 0.31 mL) in anhydrous toluene (5 mL). At 0°C, TMAD (0.21 g, 1.24 mmol) was added neat and the reaction mixture was stirred at 40°C for 15 h. TLC monitoring (SiO_2, PE/DCM, 48/1) showed formation of a new UV active compound ($R_f=0.12$). Filtration on a silica bed using EtOAc/*c*-hexane as eluant gave 244 mg of **1d** as a white solid in a 95% yield. 3,6-Dibromo-9-(2-octyl)-9*H*-carbazole **1h**. Yield 25%. Colourless oil. ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 8.1 (m, 2H), 7.5 (m, 2H), 7.4 (m, 2H), 4.6 (m, 1H), 2.2 (m, 1H), 2.0–1.8 (m, 1H), 1.6 (d, $J=7.0$ Hz, 3H), 1.3–0.9 (m, 8H), 0.8 (t, $J=6.6$ Hz, 3H). ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ (ppm) 139.0, 129.1, 124.2, 123.5, 112.1, 52.2, 35.2, 31.9, 29.3, 27.1, 22.8, 19.7, 14.3. Anal. calcd for $C_{20}H_{23}Br_2N$: C, 54.94; H, 5.30; N, 3.20. Found: C, 54.93; H, 5.33; N, 3.41%. 5-Bromo-1-oxiranylmethyl-1*H*-indole **1b**. Yield 25%. Colourless oil. ^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm) 7.7 (m, 1H), 7.6 (m, 1H), 7.4 (d, $J=3.4$ Hz, 1H), 7.3 (dd, $J=8.7$, 1.9 Hz, 1H), 6.5 (m, 1H) 4.6 (dd, $J=15.3$, 3.2 Hz, 1H), 4.2 (dd, $J=15.1$, 6.0 Hz, 1H), 3.3 (m, 1H), 2.8 (m, 1H), 2.6 (m, 1H). Anal. calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.48; H, 4.09; N, 5.52%.

11. **General procedure using CMMP**. 9-Benzyl-3,6-dibromo-9*H*-carbazole **1d**. In a 15 mL dried ACE pressure tube under an argon atmosphere, CMMP (prepared according to the protocol of Tsunoda, T.; Nagiro, C.; Oguri, M.; Ito, S. *Tetrahedron Lett*. **1996**, *37*, 2459–2462) (0.200 g, 1.74 mmol) was added into a solution of benzyl alcohol (0.188 g, 1.74 mmol, 0.18 mL) and of 3,6-dibromo-9*H*-carbazole (0.282 g, 0.87 mmol) in toluene (10 mL). The reaction mixture was stirred at 110°C for 15 h. TLC monitoring (SiO_2, PE/DCM, 48/1) showed the formation of a new UV active compound ($R_f=0.12$). Flash chromatography (SiO_2, PE/DCM, 3/1) gave 350 mg of **1d** as a white powder in a 97% yield. 9-(2-Octyl)-3-nitro-9*H*-carbazole **1i**. Yield 82%. Yellow oil. ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 9.0 (d, $J=2.26$ Hz, 1H), 8.3 (dd, $J=9.2$, 2.4 Hz, 1H), 8.2 (m, 1H), 7.6 (m, 3H), 7.3 (m, 1H), 4.8 (m, 1H), 2.3 (m, 1H), 2.0 (m, 1H), 1.7 (d, $J=7.2$ Hz, 3H), 1.4–1.0 (m, 8H), 0.9–0.7 (m, 3H). ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ (ppm) 140.6, 127.4, 123.6, 123.3, 121.6, 121.3, 120.8, 117.5, 111.3, 109.8, 109.4, 52.6, 35.2, 31.8, 29.2, 27.1, 22.8, 19.7, 14.3. Anal. calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 73.94; H, 7.48; N, 8.60%. 1-Benzyl-5-bromo-1*H*-indole **1a**. Yield 88%. White powder. Mp 70.5°C. ^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm) 7.8 (m, 1H), 7.5 (d, $J=3.2$ Hz, 1H), 7.4 (m, 1H), 7.2 (m, 6H), 6.5 (m, 1H), 5.4 (s, 2H). ^{13}C NMR: (75.5 MHz, DMSO-d_6) δ (ppm) 138.9, 135.4, 131.6, 131.0, 129.5, 128.3, 127.9, 124.5, 123.6, 113.1, 112.7, 101.6, 50.1. Anal. calcd for $C_{15}H_{12}BrN$: C, 62.96; H, 4.23; N, 4.89. Found: C, 62.99; H, 4.37; N, 4.95%. 5-Bromo-1-(2-octyl)-1*H*-indole **1c**. Yield 93%. Colourless oil. ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 7.8 (m, 1H), 7.3 (m, 2H), 7.2 (d, $J=3.2$ Hz, 1H), 6.5 (d, $J=3.2$ Hz, 1H), 4.5 (m, 1H), 2.0–1.7 (m, 2H), 1.5 (d, $J=6.8$ Hz, 3H), 1.4–1.0 (m, 8H), 0.9 (t, $J=7.1$ Hz, 3H). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ (ppm) 134.9, 130.9, 125.5, 124.3, 123.7, 112.7, 111.2, 101.3, 52.2, 37.5, 32.0, 29.4, 26.6, 22.9, 21.7, 14.4. Anal. calcd for $C_{16}H_{22}BrN$: C, 62.34; H, 7.19; N, 4.54. Found: C, 62.38; H, 7.24; N, 4.61%. 3,6-Dibromo-9-*tert*-butyl-9*H*-carbazole **1j**. In a 15 mL dried ACE pressure tube under an argon atmosphere, a solution of 3,6-dibromo-9*H*-carbazole (0.100 g, 0.308 mmol) and cyanomethyl-trimethyl-phosphonium chloride (0.584 g, 3.85 mmol) in anhydrous THF (5 mL) was treated with *t*-BuOK (0.380 g, 3.39 mmol) at 0°C. After 4.5 h at rt, the reaction mixture was stirred at 80°C. TLC monitoring (EtOAc/*c*-hexane, 1/6) showed formation of a new UV active compound ($R_f=0.42$). Flash chromatography (SiO_2, PE/DCM, 3/1) gave **1j** as a white powder in a 70% yield. Mp: 170.5°C. ^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm) 8.5 (m, 2H), 7.9 (m, 2H), 7.5 (m, 2H), 1.9 (s, 9H). ^{13}C NMR: (DMSO-d_6, 75.5 MHz) δ (ppm) 139.8, 129.3, 127.2, 125.6, 123.8, 117.0, 112.1, 60.4, 31.3.

12. The one-pot protocol using a solution of cyanomethyl-trimethyl-phosphonium chloride (2.5 equiv.), amine (1 equiv.), alcohol (2 equiv.) and KH (2.2 equiv.) in THF gave similar yields to those observed in entries 1 and 4 using the above described protocol of CMMP.