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Triton B–Mediated Mild, Convenient, and Efficient Method for the Selective Alkylation of Cyclic Secondary Amines and Thiols

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Abstract: Alkylation of cyclic secondary amines, thiols, and pyridazinones has been demonstrated with alkyl halides using Triton B as base and reaction medium.

Keywords: Alkyl halides, amines, thiols, Triton B

There are numerous methods for the N-alkylation of cyclic secondary amines. Traditionally, alkylation has been performed using alkyl halides in an organic solvent in the presence of a base. Metal amides have also been used as base for the alkylation in the presence of an excess of triethylamine.[1] Sodium hydride[2] has been reported to catalyze the alkylation of pyridazinone and pyrrolidinone under forcible conditions, which leads to a mixture of products.[2] A rapid method using potassium hydroxide (KOH)[3] and a phase-transfer catalyst under microwave irradiation[4] has been reported for exclusive N-alkylation in dry media. Alkylation of thiols has been demonstrated using alkyl halides and potassium carbonate with heating.[5] However, a method with a nonmetallic reagent using Huenig's base[6] has been reported for benzylation and butylation in an inert atmosphere. Recently, an indirect method for benzylation[7] has been published using a high-load-soluble oligomeric sulfonate ester as a benzyl equivalent under anhydrous condition.

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Based on the dry-media concept, the reagent concentration method for the synthesis of tertiary amines[8] either with or without a small amount of cosolvent has been reported to increase the yield and shorten the reaction time. However, the reported methods have the drawbacks of using strong metallic bases, which causes hydrolysis of ester and generates metal-ion-containing waste. Some of the methods use dimethylformamide (DMF) as a solvent, which requires absolutely dry conditions, tedious workup, and difficult recovery of the product. Recently, dry-media[9] reactions are an area of growing interest because of distinct advantages, such as replacement of hazardous solvent, enhanced reaction rate, easy recovery of products, and simple operation. Thus, there is a need to develop an operationally simple, safe, and widely usable method using a nonmetallic base in solvent-free conditions.

In recent years, there has been growing interest in the use of alkyl ammonium ions as phase-transfer catalysts.[10] Herein, we report the results of Triton B–mediated alkylation of secondary amines, imides, thiols, and pyridazinones.

EXPERIMENTAL

To optimize the effective conditions, the reaction of N-Boc piperazine and benzyl bromide was carried out using different ratios (1, 2, and 3 equiv.) of Triton B. With 1 equiv. of Triton B, the reaction proceeded sluggishly and took longer (12 h) for the completion of reaction. However, the efficiency of the reaction was enhanced, and reaction time was shortened (3 h) by employing 3 equiv. of Triton B. Further, keeping the advantages of dry media in mind, the reaction was performed in solvent-free conditions (by removing solvent from Triton B). To our delight, the reaction proceeded well in solvent-free condition and after extraction with ether gave only alkylated product in excellent yield. Because this solvent-free protocol is advantageous environmentally friendly, we examined a variety of substrates in solvent-free conditions. During the investigation, it was observed that 3 equiv. of Triton B was not completely utilized in reaction. This fact was further supported by the reuse of unused Triton B. The remainder of the unused Triton B along with ammonium bromide was vacuum dried and used for next reaction cycle. This exercise was repeated for three cycles, and the products were isolated with gradual decrease in the yield (96, 89, and 82%). The presence of formed ammonium bromide during reaction has the additional advantage that it may act as a "salt out" reagent, which facilitates the reaction.[11]

General Procedure

A mixture of Triton B (3 mmol) and amine/thiol (1 mmol) was stirred at rt for 15 min. Then alkyl halide (1.2 mmol) was added dropwise, and the resulting mixture was stirred at rt for the time given in (Table 1). After completion of the reaction, as indicated by thin-layer chromatography (TLC), the mixture was extracted with ether (3×15 ml). The combined organic layer washed with water and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by passing it through a small silica-gel bed to give the pure product.

Benzylation of N-Boc piperazine and homopiperazine (entries 1 and 3) proceeded expediously and delivered the N-alkylated product in excellent yield, whereas the benzylation of N-methyl piperazine (entry 2) was relatively slow. Next, we examined the 4-hydroxy-substituted piperazine (entry 5), which also showed the enhanced rate of reaction. To further determine the scope of this method, a range of secondary amines and thiols were examined (see Table 1). Nitrogen selectivity over oxygen[12] is further shown by examining the substrates with cyclic imide system. For example, alkylation of pyrrolidinone (entry 6) and 5-phenyl pyridizanone (entry 7) gives a selectively N-alkylated product. Encouraged by these results, we extended this protocol for the alkylation of thiols (entries 9 and 10) and 2-mercapto benzothiazole (entry 11) with alkyl halides, and S-alkylated products were obtained in excellent yield. The present reaction conditions for the N-alkylation is compatible with Boc and ester groups. As can be seen from Table 1, the method is applicable for a variety of secondary amines and thiols and gives the desired alkylated product in excellent yield.

Spectral Data for Selected Products

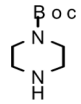
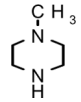
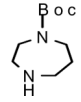
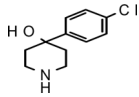
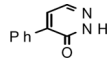
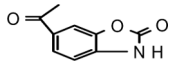
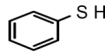
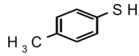
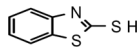
Compound **1a**

Yellow solid; mp 62–63°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.45 (s, 9H), 2.36 (t, 4H, $J = 4.532$ Hz); 3.3 (t, 4H, $J = 4.532$ Hz) 3.47 (s, 2H), 7.2 (m, 5H); EIMS m/z 299 $(M + Na)^+$, 185, 91, 77; IR (KBr) $\nu = 2972$, 2942, 1685, 1427 cm^{-1}.

Compound **5a**

Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.4 (m, 4H), 2.85 (m, 4H), 3.55 (s, 2H), 7.2 (m, 9H); EIMS m/z 303 $(M + 1)$, 302 (M^+), 224, 191, 175, 91, 77. IR (KBr) $\nu = 3382$, 3030, 2927, 2817, 1486 cm^{-1}.

Table 1. Triton B–mediated alkylation[a] of cyclic amines and thiols

Entry	Amines/thiols	Alkyl halides	Time (h)[b]	Products	Yield[c] (%)
1		a) $PhCH_2Br$	3	**1a**	96
		b) $ClCH_2COOEt$	3.5	**1b**	91
		c) n-Bu-Br	3	**1c**	94
2		a) $PhCH_2Br$	4	**2a**	89
		b) $ClCH_2COOEt$	5	**2b**	84
		c) n-Bu-Br	4	**2c**	85
3		a) $PhCH_2Br$	2	**3a**	97
		b) $ClCH_2COOEt$	2.5	**3b**	94
		c) n-Bu-Br	2.5	**3c**	95
4		a) $PhCH_2Br$	2	**4a**	95
		b) $ClCH_2COOEt$	3	**4b**	91
		c) n-Bu-Br	2	**4c**	93
5		a) $PhCH_2Br$	1.5	**5a**	97
		b) $ClCH_2COOEt$	2	**5b**	95
		c) n-Bu-Br	1.5	**5c**	96
6		a) $PhCH_2Br$	3	**6a**	92
		b) $ClCH_2COOEt$	5	**6b**	87
		c) n-Bu-Br	4	**6c**	85
7		a) $PhCH_2Br$	5	**7a**	90
		b) $ClCH_2COOEt$	5	**7b**	88
		c) n-Bu-Br	4	**7c**	90
8		a) $PhCH_2Br$	2	**8a**	93
		b) $ClCH_2COOCH_3$	3	**8b**	96
		c) n-Bu-Br	2.5	**8c**	94
9		a) $PhCH_2Br$	1.5	**9a**	96
		b) $ClCH_2COOCH_3$	2	**9b**	97
		c) n-Bu-Br	2.5	**9c**	94
10		a) $PhCH_2Br$	2	**10a**	97
		b) $ClCH_2COOEt$	2.5	**10b**	95
		c) n-Bu-Br	2.5	**10c**	94
11		a) $PhCH_2Br$	2	**11a**	97
		b) $ClCH_2COOEt$	2	**11b**	94
		c) n-Bu-Br	3	**11c**	95

[a]All the products exhibited physical and spectral (NMR, mass, IR) properties in accordance with the assigned structure.

[b]All reactions are carried out at rt only.

[c]Isolated yield.

Compound **5c**

Yellow solid; mp 95–96°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.9 (t, 3H, $J = 7.554$ Hz), 1.2 (m, 2H), 1.5 (m, 2H), 2.2 (m, 4H), 2.4 (m, 4H), 2.8 (m, 2H), 7.2 (m, 2H), 7.4 (m, 2H); EIMS m/z 291 $(M + Na)^+$, 157, 101, 76; IR (KBr) $\nu = 3371$, 2960, 1450, 1393 cm^{-1}.

Compound **7a**

Yellow solid; mp 98–99°C; ^{1}HNMR (300 MHz, $CDCl_3$) δ (ppm) 5.3 (s, 2H), 7.2–7.5 (m, 11H), 7.85 (s, 1H); EIMS m/z 285 $(M + Na)^+$, 185, 171, 91, 77; IR (KBr) $\nu = 2980$, 1650, 1580, 1375.

Compound **8b**

White solid; mp 147–148°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.5 (s, 3H), 3.7 (s, 3H), 4.6 (s, 2H), 6.9–7.7 (m, 3H); EIMS m/z 272 $(M + Na)^+$, 177, 135, 94; IR (KBr) $\nu = 3080$, 2987, 2958, 1772, 1736, 1676, 1454 cm^{-1}.

Compound **9b**

Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.59 (s, 2H), 3.7 (s, 3H), 7.2 (m, 5H); EIMS m/z 221 $(M + K)^+$, 151, 109, 77, 59; IR (KBr) $\nu = 3057$, 3000, 2952, 1738, 1438, 1278.

Compound **11a**

Semisolid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.65 (s, 2H), 7.2–7.4 (m, 5H), 7.4–7.5 (m, 2H), 7.75 (m, 1H), 7.9 (m, 1H); EIMS m/z 257 (M^+), 166, 91, 77. IR (KBr) $\nu = 3060$, 3028, 1457, 1426 cm^{-1}.

CONCLUSION

In conclusion, we have demonstrated a mild and efficient protocol for the alkylation of cyclic secondary amines, imides, pyridazinones, and thiols using Triton B as a base. The nonmetallic nature of the base and solvent-free conditions make the procedure safe and green. Moreover, the present method tolerates the presence of Boc and ester groups.

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