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1,2,3-Triazole as a safer and practical substitute for cyanide in the Bruylants reaction for the synthesis of tertiary amines containing tertiary alkyl or aryl groups

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Abstract—Tertiary amines containing tertiary alkyl or aryl groups were synthesized by the reaction of a ketone with an amine and 1,2,3-triazole followed by substitution of the triazole adduct with a Grignard reagent. Thus, 1,2,3-triazole serves as a safer and practical alternative to cyanide in the Bruylants reaction.

Tertiary amines containing tertiary alkyl group, such as 4-methyl-4-(4-alkyl-piperazin-1-yl)-piperidine-1-carboxylic acid *tert*-butyl ester, are intermediates in the synthesis of biologically important molecules.[1] Their synthesis utilized two steps, a Strecker reaction of a ketone with an amine and potassium cyanide (or diethyl aluminum cyanide) and a Bruylants reaction of resulting aminonitrile with a Grignard reagent.[2] Use of toxic cyanide reagents as well as the use of cyanide as a leaving group makes this synthesis undesirable for large-scale preparations. Benzotriazole was reported by Katritzky et al.[3] as a substitute for cyanide. However, benzotriazole is known to be an explosive reagent,[4] and in some cases, the yield of the product was poor. We were recently faced with the challenge of developing a safer and practical alternative to cyanide that is amenable for large scale. In this paper, we report 1,2,3-triazole as a safer and practical alternative to cyanide in the Bruylants reaction for the synthesis of tertiary amines containing tertiary alkyl and aryl groups that is also superior to benzotriazole. 1,2,3-Triazole is also more atom efficient than benzotriazole, and its cost in large scale is well acceptable.

We reasoned that 1,2,3-triazole and 1,2,4-triazole would be safer and practical alternatives to the cyanide in the Bruylants reaction since neither of these compounds were reported to be explosive. In addition, our own safety tests of these materials showed no hazard. Thus, the reaction of cyclohexanone with piperidine in the presence of 1,2,3-triazole in toluene at 108–114 °C with azeotropic removal of water afforded a solution of the corresponding triazolyl intermediate (**I**, Scheme 1), which was not isolated and was added to a solution of phenylmagnesium bromide at 24 °C to afford the desired product 1-(1-phenylcyclohexyl)piperidine (**1**) in 80% isolated yield (entry 1, Table 1). Similarly, methylmagnesium chloride afforded the corresponding methyl compound (**2**) in 73% yield (entry 4, Table 1). The same reaction in the presence of 1,2,4-triazole and benzotriazole gave lower yields of **1** (54% and 55%, respectively, entries 2 and 3) with phenylmagnesium bromide and of **2** (60% and 50%, respectively, entries 5 and 6) with methylmagnesium chloride. These results suggested that 1,2,3-triazole was superior to 1,2,4-triazole and benzotriazole. Similar results were obtained during the reaction of cyclohexanone with morpholine and *N*-methylpiperazine followed by the reaction of the corresponding triazolyl intermediate with phenylmagnesium bromide. The reaction of cyclohexanone with pyrrolidine in the presence of benzotriazole followed by phenylmagnesium bromide was reported[3] to afford only 13% of **5**. In our hands, we obtained a 12% yield of **5** with benzotriazole (entry 14). However, use of 1,2,3-triazole afforded **5** in 52% yield (entry 13). The yield of **6** from cyclohexanone, *N*-benzylmethylamine, and phenylmagnesium bromide was only 31% in the presence of 1,2,3-triazole (entry

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Keywords: 1,2,3-Triazole; Tertiary amines; Bruylants reaction.

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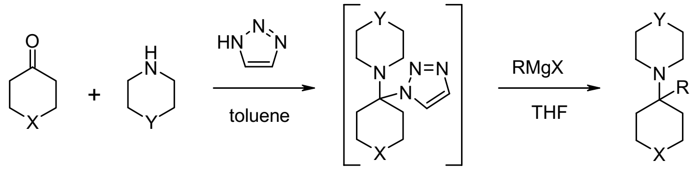
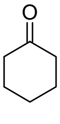
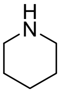
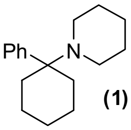
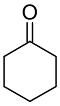
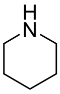
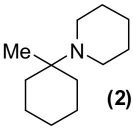
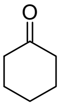
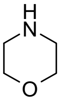
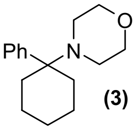
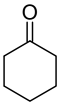
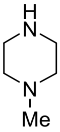
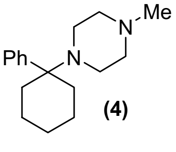
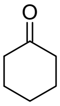
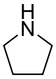
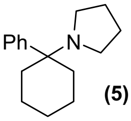
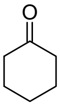
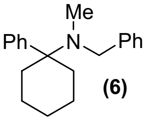


(I)

R=Me, Ph
X=CH_2, N-BOC
Y=CH_2, N-Me, O

Scheme 1.

Table 1. Comparison of triazoles with cyclohexanone

Entry	Ketone	Amine	Triazole	Grignard reagent	Product	Isolated yield (%)
1			1,2,3-Triazole	PhMgBr	 (1)	80
2			1,2,4-Triazole	PhMgBr		54
3			Benzotriazole	PhMgBr		55
4			1,2,3-Triazole	MeMgCl	 (2)	73
5			1,2,4-Triazole	MeMgCl		60
6			Benzotriazole	MeMgCl		50
7			1,2,3-Triazole	PhMgBr	 (3)	84
8			1, 2,4-Triazole	PhMgBr		68
9			Benzotriazole	PhMgBr		67
10			1,2,3-Triazole	PhMgBr	 (4)	74
11			1,2,4-Triazole	PhMgBr		57
12			Benzotriazole	PhMgBr		53
13			1,2,3-Triazole	PhMgBr	 (5)	52
14			Benzotriazole	PhMgBr		12
15		$PhCH_2NHMe$	1,2,3-Triazole	PhMgBr	 (6)	31
16			1,2,4-Triazole	PhMgBr		25
17			Benzotriazole	PhMgBr		20

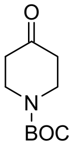
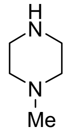
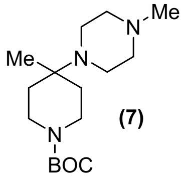
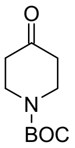
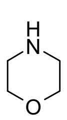
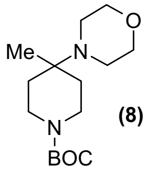
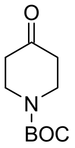
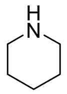
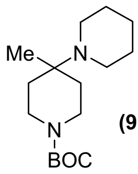
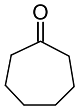
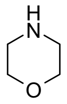
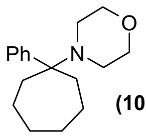
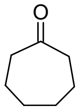
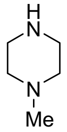
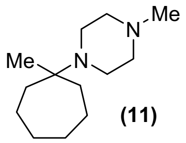
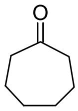
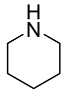
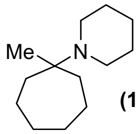
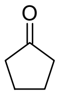
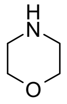
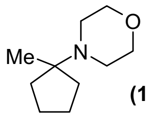
15), nevertheless it was better than those obtained with 1,2,4-triazole and benzotriazole, which were 25% and 20%, respectively (entries 16 and 17).

The synthetic utility of 1,2,3-triazole was further studied with several ketones and amines, and the results are listed in Table 2. Six-membered ketones gave excellent yield with various amines (entries 1–3, Table 2). The reaction of cycloheptanone with morpholine and benzotriazole, followed by the treatment of the adduct with phenylmagnesium bromide was reported[3] to afford only 13% yield of **10**. However, the yield of **10** with 1,2,3-triazole was 45% (entry 4). These results further confirmed the superiority of 1,2,3-triazole over benzotriazole. The yields of **11** and **12** from cycloheptanone in the presence of 1,2,3-triazole were also modest (entries 5 and 6, Table 2). Reaction of cyclopentanone with morpholine in the presence of benzotriazole and subsequent reaction of the resulting adduct with methylmagnesium bromide was reported[3] to afford only the enamine as the major product. This reaction in the presence of 1,2,3-triazole afforded the desired product in 38% yield (entry 7). These results once again suggested that 1,2,3-triazole is superior to benzotriazole.

In summary, 1,2,3-triazole is a safer and practical alternative to cyanide in the Bruylants reaction for the synthesis of tertiary amines containing tertiary alkyl or aryl groups. The scope of this reaction will be further studied with other ketones and Grignard reagents.

Typical experimental procedure: A three-necked flask, equipped with a mechanical stirrer, a Dean–Stark trap, a condenser with nitrogen inlet–outlet was charged with

Table 2. Reaction with 1,2,3-triazole

Entry	Ketone	Amine	Triazole	Grignard reagent	Product	Isolated yield (%)
1			1, 2,3-Triazole	MeMgCl	 **(7)**	79
2			1,2,3-Triazole	MeMgCl	 **(8)**	90
3			1,2,3-Triazole	MeMgCl	 **(9)**	85
4			1, 2,3-Triazole	PhMgBr	 **(10)**	45 (13)[a]
5			1, 2,3-Triazole	MeMgCl	 **(11)**	40
6			1,2,3-Triazole	MeMgCl	 **(12)**	40
7			1, 2,3-Triazole	MeMgCl	 **(13)**	38

[a] Yield reported in Ref. 4.

an amine (55 mmol), ketone (50 mmol), 1,2,3-triazole, or 1,2,4-triazole, or benzotriazole (60 mmol) and 50 mL of toluene. The reaction mixture was heated to 108–114 °C to achieve reflux and stirred for 6–8 h while collecting water via a Dean–Stark trap. The reaction mixture was cooled to room temperature and added to phenylmagnesium bromide (200 mmol, 1 M in THF) or methylmagnesium chloride (200 mmol, 3 M in THF) over a period of 30 min with efficient stirring while maintaining the internal temperature at <24 °C. The reaction mixture was stirred at room temperature for an additional 1 h. It was then added to a 20% ammonium chloride solution (120 g) over a period of 30 min while maintaining the internal temperature at <30 °C. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were washed with 2 N sodium hydroxide (100 mL), water (100 mL), and concentrated. The crude material was purified by silica gel chromatography to afford compounds **1**–**13**. All the compounds gave satisfactory spectral and analytical data. Compounds **1**, **3**, **5**, and **10** are cataloged chemicals. Compounds **2**, **4**, and **12** are known in the literature.[5]

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5. For compound **2** and **12**, see Lynch, P. P.; Doyle, P. H. *Gazzetta Chimica Italiana* **1968**, *98*, 645–655. For compound **4**, see Ref. 2a.