The Direct Carbamoylation of Organometallic Reagents with 1,2,3-Benzotriazole -1-carboxamides†

J. Chem. Research (S), 1999, 230–231†

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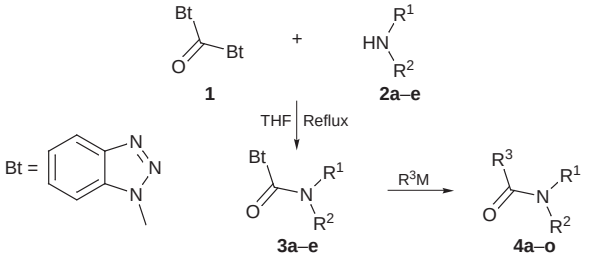
Various (hetero)aromatic amides are synthesized efficiently by the carbamoylation of organometallic reagents.

Tertiary aromatic and heterocyclic carboxamides are important bioactive agents showing activity as antifungal agents,[1] squalene epoxidase inhibitors,[2] melatonin analogs,[3] potential anti-HIV drugs, and antitumor agents.[4]

Many tertiary carboxamides are prepared by the electrophilic acylation of amines.[5] However, instead of the formation of the CO–N bond, it is sometimes convenient to construct tertiary amides by C–CON bond formation. Three main variants of this strategy have been reported: (i) the coupling of organometallics with carbamoyl chlorides,[6–8] (ii) an alternative homolytic amidation of aromatic compounds which is limited to protonated heteroaromatics,[9] and (iii) metal-catalyzed carbonylation reactions of organic halides,[10,11] often under tuned conditions.[12,13]

The leaving group properties of benzotriazole[14] suggested a possible utility of 1,1′-carbonylbisbenzotriazole for *N*-carbamoylation. The utility of this reagent in enabling the successive substitution of two benzotriazole moieties with *N*-nucleophiles was recently demonstrated by general syntheses of unsymmetrical tetrasubstituted ureas[15] and oxamides.[16]

We now report the carbamoylation reaction of carbanions with *N,N*-disubstituted-1,2,3-benzotriazole-1-carboxamides as a new synthetic pathway to (hetero)aryl amides as shown in Scheme 1. Intermediates **3a**–**e** were prepared by the reaction of 1.1 equiv. of the corresponding secondary amines **2a**–**e** with 1.0 equiv. of 1,1′- carbonylbisbenzotriazole **1** which yielded the corresponding *N,N*-disubstituted-1,2,3-benzotriazole-1-carboxamides **3a**–**e** (Table 1). Increasing the reported reaction time[15] improved the yield of intermediate **3b** and enabled synthesis of compound **3c**, a precursor of reportedly bioactive tetrahydroisoquinoline amides.[17]



Scheme 1 (R^1, R^2=alkyl, aryl; R^3 = aryl, heteroaryl; M = Mg, Li).

Carbamoylation of aryl Grignard reagents with intermediates **3a**–**e** led to tertiary carboxamides **4a**–**i** (Table 2). Diaryl-(**4a**) and *N*-aryl-*N*-alkylamides (**4b**–**i**) were obtained in high yields. Aryl Grignards substituted with an electron withdrawing group (4-Cl) (**4f**,**g**) afforded good yields in THF while aryl Grignards substituted with an electron-donating group (Me) required toluene to achieve good yields (**4h**,**i**). Heterocyclic lithio-derivatives (generated from the corresponding heterocycle and Bu^nLi by lithiation procedures[18–20] were reacted with intermediates **3** to yield heterocyclic amides **4j**–**o** in moderate to good yields, as shown in Table 2. Attempts with alkyl Grignard reagents at room temperature provided only starting materials after a few hours; when heated to reflux temperature, decomposition occurred. Alkyl zinc reagents also failed.

In summary, the benzotriazole moiety of compounds **3a**–**e** was readily displaced by organometallic reagents (Grignard or lithio derivatives) to yield the desired benzamides or heterocyclic amides in moderate to good yields.

Table 1 Preparation of *N,N*-disubstituted-1,2,3-benzotriazole-1-carboxamides **3a**–**e**

	R^1	R^2	Yield (%)	Mp (lit. mp)/°C	Found (Calc.) (%) C	H	N
3a	Ph	Ph	22	100–102 (103–105)			
3b	Ph	Me	68	75–77 (76–78)			
3c	—[a]	—[a]	72	109–111	69.03 (69.04)	5.19 (5.08)	20.30 (20.14)
3d	4-MeC_6H_4	Me	80	57–59	67.55 (67.55)	5.12 (5.31)	21.16 (21.04)
3e	$(CH_2)_2O(CH_2)_2$		74	101–102 (102–103)			

[a] = 1,2,3,4-Tetrahydroisoquinoline-2-yl.

Experimental

Compounds **3a**–**e** were prepared by the procedure reported in ref. 15.

General Procedure for the Preparation of Amides **4a**–**i**.—To a solution of **3a**–**e** (1 mmol) under nitrogen in 10 ml of dry THF (or toluene) was added the corresponding Grignard reagent (2 mmol).

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

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Table 2 Preparation of alkyl, aryl and heterocyclic amides **4**

	R^1	R^2	R^3	Yield(%)	Mp (lit. mp)/°C	Found (Calc.) (%) C	H	N
4a	Ph	Ph	Ph	81	163 (177)[21]	(83.48)	(5.54)	5.32 (5.13)
4b	Ph	Me	Ph	75	Oil[7]	79.24 (79.59)	6.39 (6.21)	6.93 (6.63)
4c	—[a]	—[a]	Ph	78	Oil[22]	(80.98)	(6.38)	5.87 (5.90)
4d	4-MeC_6H_4	Me	Ph	83	Oil[23]	79.88 (79.96)	6.88 (6.72)	6.64 (6.22)
4e	$(CH_2)_2O(CH_2)_2$		Ph	81	Oil[24]	(69.08)	(6.87)	6.94 (7.33)
4f	Ph	Me	4-ClC_6H_4	93	Oil[25]	68.23 (68.43)	4.98 (4.93)	5.49 (5.70)
4g	—[a]	—[a]	4-ClC_6H_4	93	Oil	(70.71)	(5.20)	5.10 (5.16)
4h	Ph	Me	4-MeC_6H_4	90	Oil[7]	(79.96)	(6.72)	6.15 (6.22)
4i	—[a]	—[a]	4-MeC_6H_4	89	Oil	(81.24)	(6.83)	5.55 (5.57)
4j	Ph	Me	—[b]	58	115[26] —[e]	71.65 (71.88)	4.97 (4.91)	5.39 (5.24)
4k	—[a]	—[a]	—[b]	60	Oil	(73.68)	(5.16)	4.55 (4.78)
4l	$(CH_2)_2O(CH_2)_2$		—[b]	71	94 —[f]	(69.13)	(5.31)	5.33 (5.66)
4m	Ph	Me	—[c]	31	Oil[27]	(74.24)	(6.11)	10.42 (10.60)
4n	—[a]	—[a]	—[c]	26	123 —[g]	78.22 (78.59)	6.24 (6.26)	9.58 (9.65)
4o	—[a]	—[a]	—[d]	60	Oil	(69.68)	(6.28)	17.03 (17.42)

[a] 1,2,3,4-tetrahydroisoquinoline-2-yl. [b] Benzo[*b*]thiophene-2-yl. [c] 1-Methylindole-2-yl. [d] 1-Methylimidazole-2-yl. [e] Not reported, [f] Patent (*Chem. Abstr.,* 1995, **122**, 239533a]. [g] New compound.

After completion of the reaction (TLC), the reaction mixture was hydrolyzed by NH_4Cl (50%) and extracted with ethyl acetate (3×10 ml). The organic layers were dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. The resulting oil was subjected to column chromatography (silica gel; eluent: hexanes–ethyl acetate) to give the pure products **4a**–**i**. The compounds were characterized by NMR (^1H, ^{13}C) and elemental analysis (Table 2).

General Procedure for the Preparation of Amides **4j**–**o**.—To the corresponding heterocycle (1 mmol) in 10 ml of dry THF under nitrogen was added dropwise Bu^nLi (1 mmol) at −78 °C. The resulting solution was stirred for 15 min, and compound **3a**–**e** (1 mmol) in dry THF (10 ml) was added dropwise. The mixture was stirred at −78 °C for 16 h and then allowed to warm to 20 °C. After quenching with H_2O (5 ml) and extraction with Et_2O (3×10 ml), the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The resulting oil was purified by column chromatography (silica gel; eluent: hexanes–ethyl acetate) to give the pure products **4j**–**o**. The compounds were characterized by NMR (^1H, ^{13}C) and elemental analysis (Table 2).

Received, 24th November 1998; Accepted 15th December 1998
Paper E/8/09181A

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