Synlett R. Lira et al. Letter

Cyclic 1-(Arylamino)carboxylates via Mild Diastereospecific Jocic-Type Reaction with 2,2,2-Trichloromethyl Carbinols and Anilines

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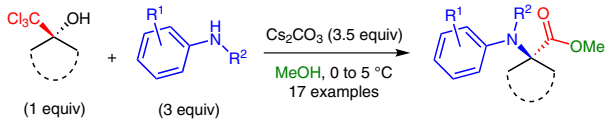


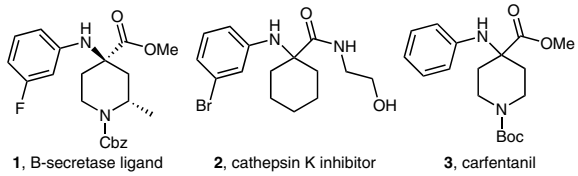
Received: 29.07.2016
Accepted after revision: 19.09.2016
Published online: 06.10.2016
DOI: 10.1055/s-0036-1588330; Art ID: st-2016-r0493-l

Abstract A mild, practical Jocic-type rearrangement for the synthesis of cyclic 1-(arylamino) carboxylates from readily available 2,2,2-trichloromethyl carbinols and anilines is described. The method demonstrates good scope, with a large variety of anilines providing direct access to several novel cyclic 1-(arylamino) carboxylates. The reaction is robust and has been shown to provide comparable results on kilogram scale. The reaction is diastereospecific, leading to the formation of a single diastereomer when utilizing stereodefined 2,2,2-trichloromethyl carbinol cores.

Key words Jocic rearrangement, 2,2,2-trichloromethyl carbinols, cyclic 1-(arylamino) carboxylates, diastereospecific, anilines

The cyclic 1-(arylamino) carboxylate functionality is an important moiety found in a variety of precursor compounds with pharmaceutical value (Figure 1).[2] Among the most common strategies to access such structures are the Strecker reaction[3] and the metal-catalyzed N-arylation of hindered α-amino carbonyl precursors (Scheme 1).[4] Most recently, Read de Alaniz reported a procedure involving a copper-catalyzed radical addition to aryl nitroso species from α-bromo esters.[5,6] However, despite the mild conditions of this protocol, which allows a variety of functional groups, the cost and safety associated with handling and isolating the highly reactive nitroso species as well as the use of SmI_2 limits its practicality for large-scale applications.

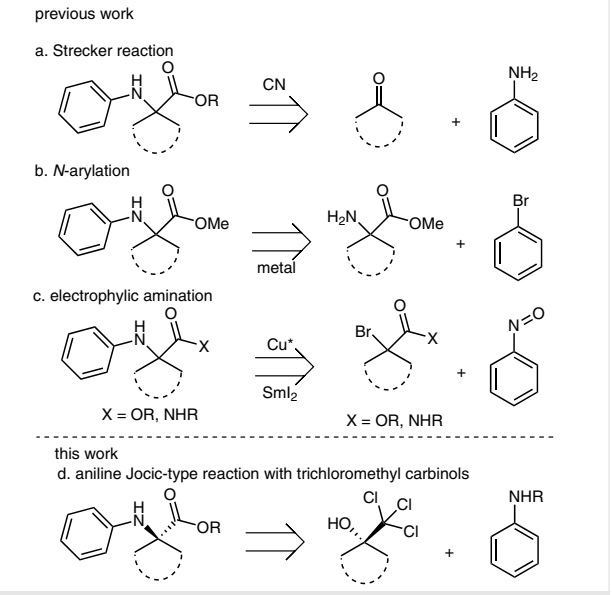
As part of an internal drug-discovery effort, we recently disclosed an example of a chemical transformation to access the key methyl 2-alkyl-2-(arylamino) acetate intermediate **1** from the readily accessible 2,2,2-trichloromethyl carbinol **4**.[2b,7,8] The reaction conditions were mild and reproducible on large scale providing more than 1 kilogram



1, B-secretase ligand precursor
2, cathepsin K inhibitor precursor
3, carfentanil precursor

Figure 1 Examples of cyclic 1-(arylamino) carboxylate motifs in precursors of compounds with pharmaceutical value

of β-secretase ligand precursor **1**.[2b,9] Formation of product **1** has been proposed to proceed via a Jocic-type rearrangement involving a transient *gem*-dichlorooxirane, followed



Scheme 1 Common strategies to access cyclic 1-(arylamino) carboxylates and this work

by an *anti* diastereospecific nucleophilic attack at the no-chloride-bearing oxirane quaternary center by the aniline nitrogen leading to an acylchloride species which is then trapped with methanol.[2a,b,10]

Herein we demonstrate the substrate scope of this procedure for the preparation of cyclic 1-(arylamino) carboxylates utilizing readily available 2,2,2-trichloromethyl carbinols and a variety anilines with a focus on piperidine-2,2,2-trimethyl carbinol core **4**.[2a,b,10]

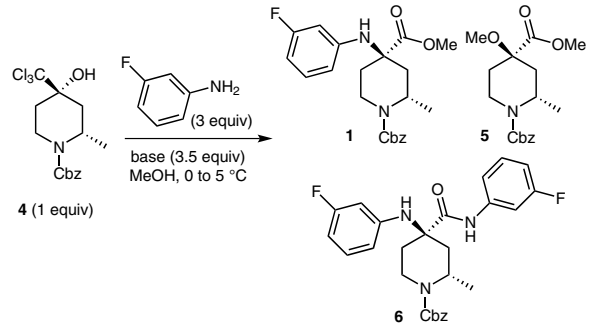
We initiated reaction optimization by evaluating a diverse set of both organic (amines) and inorganic bases. The purpose was to go beyond the 'preferred' bases previously disclosed for related transformations.[2a,11] The effectiveness of each base was assessed by measuring the relative ratios of starting material **4** to product **1** along with known side products methoxy-methyl ester **5** and amide **6** (Table 1). Pyridine-like amines (entries 1–3), as well as both cyclic alkyl (entries 4–6) and acyclic alkyl-amines (entries 7 and 8) proved to be ineffective and led to only trace amounts of desired product formation (**1**).

More strongly basic cyclic amines, such as DBU (entry 10), DBN (entry 9), and TBD (entry 12) proved superior with complete starting material consumption and varying degrees of side-product formation observed. Ultimately, DBU was determined to be the most effective organic base for the desired transformation.

Subsequently, a small set of anionic bases was screened, as shown in Table 1 (entries 13–24). Unexpectedly, cesium carbonate was found to be the base with the best reaction profile of all the bases screened, including the organic bases, leading to complete starting material consumption and minimal side-product formation. In contrast, stronger bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium methoxide, and potassium *tert*-butoxide (entries 19–24) led to the formation of significant amounts of side product **5**.

With cesium carbonate identified as the optimum base, the scope of the reaction was evaluated with various anilines and the 2,2,2-trichlomethyl carbinol **4** (Table 2). In general, anilines with a single 2-, 3-, or 4-aryl substituent performed well under the optimized reaction conditions, leading to 64–79% isolated yields of the desired products (entries 1–5, 9). A slight decrease in yield was seen with 2, 4-difluoroaniline (entry 6, 58%), electron-rich 4-dimethylaniline (entry 8, 31%) and 1-methyl-5 amino indole (entry 13, 25%). Interestingly, the bulky 2-*tert*-butyl aniline also provided the desired product, albeit in a modest 30% isolated yield (entry 10). *N*-Methyl-*N*-phenylaniline also led to lower yield (entry 11, 31%), while the *N*,*N*-biphenyl aniline in entry 12, resulted in recovered starting material **4** and no detectable product. All products shown in Table 2 were isolated as a single diastereomer, further demonstrating the utility of the transformation.[2b,12]

Table 1 Organic and Inorganic Base Screen with Substrate **4** and 3-Fluoroaniline; Crude HPLC Ratios

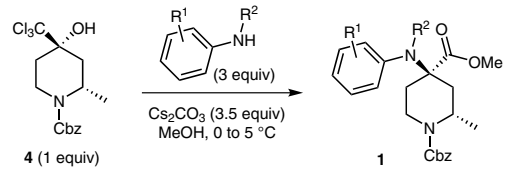


Entry	Base	Starting material **4**	Product **1**	Side product **5**	Side product **6**
1	pyridine	>98	0	0	0
2	lutidine	>96	0	0	0
3	collidine	>96	0	0	0
4	*N*-methylmorpholine	94	6	0	0
5	*N*-methylpiperidine	94	4	2	0
6	*N*-methylpyrrolidine	95	5	0	0
7	Et_3N	100	0	0	0
8	DIPEA	95	5	0	0
9	DBN[a]	0	75	16	3
10	DBU[b]	0	77	9	3
11	tetramethyl guanidine	7	81	9	3
12	TBD[c]	0	82	15	3
13	NaOAc	92	8	0	0
14	$NaHCO_3$	88	7	5	0
15	Ag_2CO_3	100	0	0	0
16	Na_2CO_3	83	5	0	12
17	K_2CO_3	7	80	8	5
18	Cs_2CO_3	0	86	11	2
19	LiOH	0	75	24	0
20	NaOMe	0	78	17	0
21	KO*t*-BU	0	41	22	0
22	NaOH	0	74	25	<1
23	KOH	70	11	19	0
24	TBAH[d]	0	9	91	0

[a] DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.
[b] DBU = 1,8-diazabicyclo]5.4.0]undec-7-ene.
[c] TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.
[d] TBAH = 1.5 M solution of tetrabutylammonium hydroxide in water.

In order to explore the scope of the reaction with other carbinol substrates, the symmetric cyclohexyl carbinol substrate **7** was evaluated with both electron-deficient and electron-rich anilines. Treatment of carbinol **7** under the optimized conditions, with electron-deficient 4-trifluoromethyl- and 3-nitroaniline provided the desired products **8**

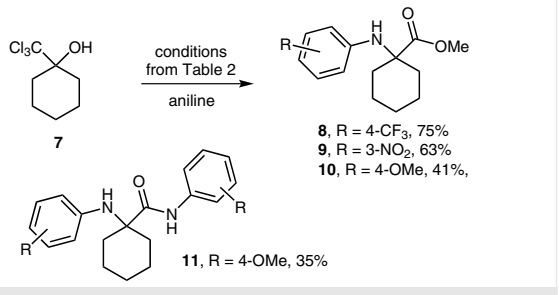
Table 2 Scope of Anilines under the Optimized Conditions



Entry	Compd	R^1	R^2	Yield (%)[a,b]
1	**1**	3-fluoro	H	76
2	**1a**	2-fluoro	H	76
3	**1b**	2-chloro	H	79
4	**1c**	4-chloro	H	74
5	**1d**	3-cyano	H	64
6	**1e**	2,4-difluoro	H	58
7	**1f**	3,4-dimethyl	H	73
8	**1g**	4-*N*,*N*-dimethyl	H	31
9	**1h**	2-phenyl	H	76
10	**1i**	2-*tert*-butyl	H	30
11	**1j**	H	Me	31
12	**1k**	H	Ph	0
13	**1l**	1-methyl-1*H*-indol-5-amine		25

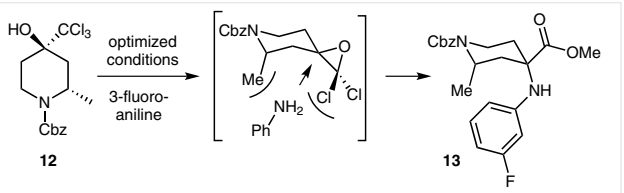
[a] Isolated yield.
[b] Products isolated as a single diastereomer.

and **9** in 75% and 63% yield, respectively (Scheme 2). The use of the electron-rich 4-OMe-aniline led to desired product **10**, but in a reduced yield (41%), due to the competitive formation of the amide side product **11** (35%).



Scheme 2 Cyclohexyl-derived analogues

To further support the diastereospecific nature of this transformation, 4-*epi*-carbinol **12** was subjected to the optimized reaction conditions (Scheme 3). From the reaction, epimer **13** emerged as the sole diastereomer in 56% isolated yield, though in lower yield than that obtained with carbinol **4** (**1**, Table 1, 76%).[13] The nucleophilic attack of the aniline from the congested bottom side of the ring highlights the high degree of stereofidelity for the transformation leading to the formation of a single cyclic 1-(arylamino) carboxylate diastereomer when starting with stereodefined 2,2,2-trichloromethyl carbinols.



Scheme 3 Support of diastereospecificity with epimer **12**

In conclusion, a mild and practical method for the synthesis of cyclic 1-(arylamino) carboxylates is described.[14] The method uses readily available 2,2,2-trichloromethyl carbinols and proceeds well with a large variety of aniline and aniline-like partners. The robustness of the reaction has been previously demonstrated in the preparation of >1 kilogram of intermediate **1**. Furthermore, the reaction was found to be diastereospecific, leading to the formation of a single diastereomer when utilizing stereodefined 2,2,2-trichloromethyl carbinol templates. Thus, based on the above features, we anticipate this transformation to be of great utility.

Acknowledgment

The authors acknowledge Yvette Fobian, Anabella Villalobos, Chris Helal, Mike Brodney, and Brian O'Neill for supporting this research.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588330.

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(12) For all products, a single diastereomer was detected by HPLC. Stereochemistry was assigned by analogy to product **2**.[2a,b]
(13) The lower yield is attributed to the competing formation of side product methoxy methyl ester of the type of **5** (Table 1). Side product was detected by mass (UPLC/MS) and was not isolated/characterized.
(14) **General Experimental Procedure**

Preparation of (2*S*,4*R*)-1-Benzyl 4-Methyl 4-(3-Cyanophenylamino)-2-methylpiperidine-1,4-dicarboxylate (1d, Table 2, Entry 5) from (2*S*,4*S*)-4-Hydroxy-2-methyl-4-(trichloromethyl)piperidine-1-carboxylate (4)

To a 20 mL vial equipped with a stir bar was charged with (2*S*,4*S*)-benzyl 4-hydroxy-2-methyl-4-(trichloromethyl)piperidine-1-carboxylate (**4**, 367 mg, 1 mmol), MeOH (2 mL), and 3-aminobenzonitrile (354 mg, 3 mmol). The resulting homogeneous reaction mixture was placed in a precooled plate at 0 °C and was stirred for 10 min. To the cooled reaction mixture was added Cs_2CO_3 (1.2 g, 3.5 mmol) in two portions over a period of about 10 min. The mixture was then warmed to 5 °C and stirred for 42 h. The reaction mixture was removed from the cold bath and was concentrated under reduced pressure in the rotavap to a gum. To the crude reaction mixture was then added MTBE (10 mL) and was transferred to an extraction funnel with MTBE (10 mL). The cloudy solution was washed with 0.5 N HCl (2 × 5 mL) and brine (5 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure in the rotovap. The resulting crude material was purified twice by silica gel flash chromatography (isco CombiFlash purification system, 24 g HP silica column, 0–60% EtOAc–heptane) and provided compound **1d** as a gum in 64% yield (268 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.37 (m, 5 H), 7.17–7.21 (m, 1 H), 7.01–7.03 (m, 1 H), 6.76–6.77 (m, 1 H), 6.73 (ddd, *J* = 8.0, 2.4, 0.8 Hz, 1 H), 5.14 (s, 2 H), 4.34–4.39 (m, 1 H), 4.21 (s, 1 H), 4.07 (ddd, *J* = 14.0, 5.6, 2.4 Hz, 1 H), 3.70 (s, 3 H), 3.27 (ddd, *J* = 14.4, 12.4, 4.0 Hz, 1 H), 2.60–2.64 (m, 1 H), 2.19 (ddd, *J* = 14.0, 5.6, 1.2 Hz, 1 H), 2.07 (dd, *J* = 13.6, 6.0 Hz, 1 H), 1.70 (ddd, *J* = 13.6, 12.4, 5.6 Hz, 1 H), 1.15 (d, *J* = 6.8 Hz, 3 H). ^{13}C (100 MHz, $CDCl_3$): δ = 174.5, 155.1, 145.4, 136.6, 129.9, 128.4, 128.0, 127.8, 122.3, 119.2, 119.0, 117.6, 112.9, 67.1, 57.5, 52.6, 45.6, 38.6, 36.1, 33.1, 17.7. ESI-HRMS: *m/z* calcd for $C_{23}H_{25}N_3O_4$ $[M + H]^+$: 408.1918; found: 408.1918.