ORGANIC LETTERS

2013
Vol. 15, No. 4
902–905

XtalFluor-E, an Efficient Coupling Reagent for Amidation of Carboxylic Acids

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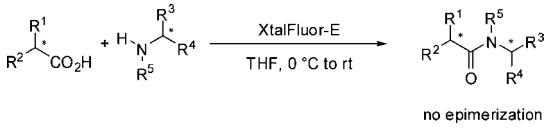
Received January 7, 2013

ABSTRACT



Amides were produced from carboxylic acids and amines by using XtalFluor-E as an activator. Even poorly reactive carboxylic acids can be transformed to amides. In addition, optically active amines and/or carboxylic acids were not epimerized/racemized during the process.

The conversion of carboxylic acids to the corresponding amides is an important transformation.[1] It has been reported by three leading pharmaceutical companies that the production of an amide bond was required in the synthesis of 65% of the drug candidates surveyed.[2] Numerous synthetic methods have been developed to synthesize amides from carboxylic acids and amines using various reactive coupling reagents.[1,3] Despite the variety of coupling reagents, the reaction conditions can be drastic (requiring elevated temperatures), the workup can be problematic, and epimerization/racemization of the substrates can occur, particularly when DCC is used. It is of interest to develop alternative conditions and/or to find new coupling reagents which are efficient and mild, which do not induce epimerization/racemization of optically active substrates and for which the workup is easy.

Herein, we would like to report that XtalFluor-E[4−6] [$(F_2SNEt_2)BF_4$] can be utilized as a reactive coupling reagent to produce amides from carboxylic acids and amines under mild conditions (THF, 0 °C to rt) and with an easy workup (Na_2CO_3, H_2O). This coupling reagent has been used to couple optically active substrates without epimerization/racemization.

Our optimization of the reaction conditions involved us studying the amidation of octan-1-oic acid **1** with benzylamine **2**. The best conditions for obtaining amide **3** entailed us using 1.5 equiv of XtalFluor-E and 2 equiv of benzylamine, at 0 °C to rt for 4 h and at a concentration of 6×10^{-2} mol/L which allowed the isolation of amide **3** in 96% yield (Table 1, entry 4). It is worth pointing out that 1.1 equiv or 1.5 equiv of amine can be used as well as 1.05 equiv of XtalFluor-E. However, the yield in **3** is not as good as with 1.5 equiv of XtalFluor-E and 2 equiv of **2** (Table 1, entries 1−3). Furthermore, increasing the number of equivalents of benzylamine (5 equiv) did not increase the yield of **3** (88%) (Table 1, entry 6).[7]

The reaction is general, and the results are reported in Table 2. XtalFluor-E can be utilized to transform aromatic

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(1) (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852. (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631. (c) Joullié, M. M.; Lassen, K. M. *ARKIVOC* **2010**, 189–250. (d) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557–6602.

(2) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(3) (a) Lee, K. S.; Kim, K. D. *Synth. Commun.* **2011**, *41*, 3497–3500 and references cited. (b) Luo, Q.-L.; Lv, L.; Tan, J.-P.; Nan, W.; Hui, Q. *Eur. J. Org. Chem.* **2011**, 6916–6922 and references cited. (c) Tian, J.; Gao, W.-C.; Zhou, D.-M.; Zhang, C. *Org. Lett.* **2012**, *14*, 3020–3023.

(4) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050–5053. (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401–3411.

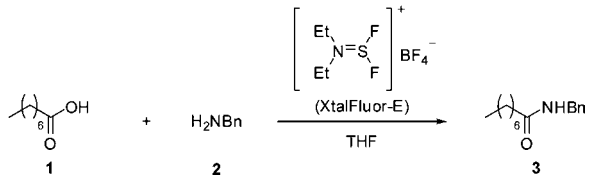
(5) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2011**, *13*, 4442–4445. Cochi, A.; Gomez Pardo, D.; Cossy *J. Eur. J. Org. Chem.* **2012**, 2023–2040.

(6) (a) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 988–993. (b) Pouliot, M.-F.; Mahé, O.; Hamel, J.-D.; Desroches, J.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5428–5431.

(7) It is worth pointing out that *N,N*-diethylamide **8** was formed in the reaction medium and the amount of **8** depends on the conditions.

10.1021/ol400045d
Published on Web 02/05/2013

Table 1. Optimization of the Reaction Conditions for the Amidation of Octan-1-oic Acid by Benzylamine



entry	2 (equiv)	XtalFluor-E (equiv)	temp (°C)	time	yield of 3[a]
1	1.1	1.05	0 °C to rt	4 h	66%
2	1.5	1.05	0 °C to rt	4 h	71%
3	1.6	1.5	0 °C to rt	4 h	76%
4	**2**	**1.5**	**0 °C to rt**	**4 h**	**96%**
5	2	1.5	0 °C	30 min	89%
6	5	1.5	0 °C	30 min	88%
7	2	1.5[b]	0 °C to rt	4 h	76%

[a] XtalFluor-E was added to a mixture of octan-1-oic acid and benzylamine. [b] XtalFluor-M was used instead of XtalFluor-E.

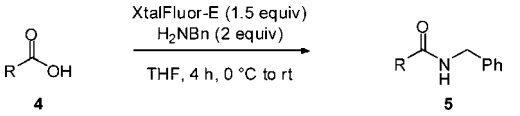
and heteroaromatic carboxylic acids **4a**–**4c** to the corresponding amides **5a**–**5c** in yields comprised between 53% and 82% (Table 2, entries 1–3). Sensitive acids such as but-3-enoic acid **4d** were transformed into amide **5d** (88%), when treated with benzylamine, without formation of the corresponding conjugated amide (Table 2, entry 4). In addition, sterically hindered carboxylic acids such as **4e** and **4f** were converted to **5e** and **5f** in excellent yields (86% and 84% respectively) (Table 2, entries 5–6). In the case of deactivated acids such as **4g** and **4h**, amides **5g** and **5h** were isolated in 67% and 52% yield respectively (Table 2, entries 7–8).

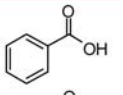
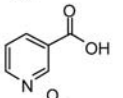
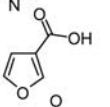
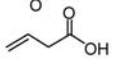
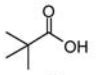
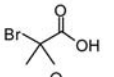
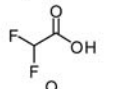
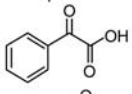
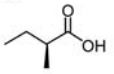
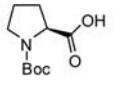
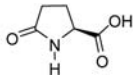
Furthermore, optically active carboxylic acids **4i** and **4j** were converted to the corresponding amides **5i** and **5j** in 91%–97% and 52%–67% yields respectively without any racemization of the carboxylic acids[8] (Table 2, entries 9–10). In addition, unprotected L-pyroglutamic acid was converted to **5k** in 84% yield (Table 2, entry 11).

A diversity of primary and secondary amines can be utilized for the amidation of carboxylic acids. The results are summarized in Table 3. Primary amines such as **6a**–**6d** led to the corresponding amides in good yields (up to 97% yield) (Table 3, entries 1–4). We have to point out that *N*-tosylamides are not reactive under these conditions, with *N*-tosyl-1,2-diaminoethane **6d** leading only to **7d** in 94% yield (Table 3, entry 4). Various anilines also engaged in the coupling process with **6e**–**6g** were transformed into the corresponding amides **7e**–**7g** in yields varying from 53% to 74% (Table 3, entries 5–7). Alkyl amines were more reactive than anilines, with octanoic acid **1** being converted to **7h** and **7h′** in 62% yield, in a ratio of 91:9, using aniline **6h** (Table 3, entry 8). When an optically active primary amine such as **6i** was coupled with carboxylic acid **1**, the

(8) The ee's were determined by SFC (Daicel chiralcel AD-H column, P = 100 bar, flow = 5 mL/min).

Table 2. Generalization: Amidation of Various Carboxylic Acids



entry	carboxylic acid 4	amide 5 (yield[a]; ee)
1	**4a** 	**5a** (82%)
2	**4b** 	**5b** (73%)
3	**4c** 	**5c** (53%)
4	**4d** 	**5d** (88%)
5	**4e** 	**5e** (86%)
6	**4f** 	**5f** (84%)
7[b]	**4g** 	**5g** (67%)
8[c]	**4h** 	**5h** (52%)
9	**4i** 	**5i** (91–97%; ee > 99%)[8]
10	**4j** 	**5j** (52–67%; ee > 99%)[8]
11	**4k** 	**5k** (84%)

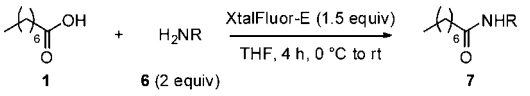
[a] Isolated yields. [b] Amide **5g** was isolated after 30 min. [c] 1.1 equiv of XtalFluor-E and 2 equiv of benzylamine were used.

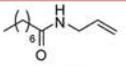
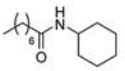
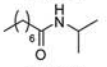
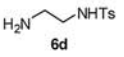
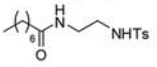
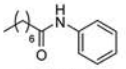
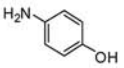
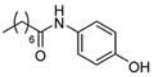
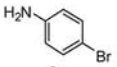
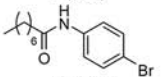
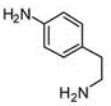
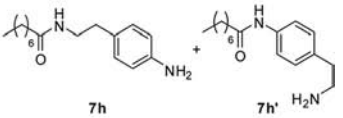
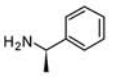
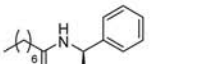
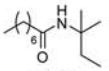
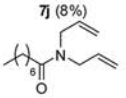
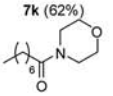
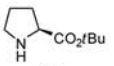
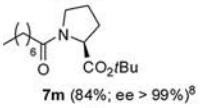
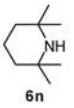
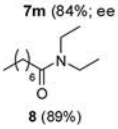
corresponding amide **7i** was isolated in 74% yield with an excellent enantiomeric excess (ee > 99%)[8] (Table 3, entry 9). One limitation was observed with sterically hindered primary amines as **6j** was converted to amide **7j** in only 8% yield. Here, the major product formed was diethylamide **8** (ratio **7j:8** = 13:87) (Table 3, entry 10). XtalFluor-E can also induce a coupling reaction between carboxylic acid **1** and different secondary amines **6k**–**6m** to produce the corresponding amides **7k**–**7m** in good yields (62–98%) (Table 3, entries 11–13). However, as previously observed, sterically hindered secondary amines such as **6n** were not reactive and diethylamide **8** was formed instead in 89% yield (Table 3, entry 14).

When sterically hindered or desactivated amines were used, diethylamide **8** was the major product and this side product constitutes a limit for the amidation of carboxylic acids using XtalFluor-E as the activating agent.

When the amidation of octan-1-oic acid **1** was studied with dibenzylamine using XtalFluor-E as the activating

Table 3. Generalization: Amidation with Primary and Secondary Amines

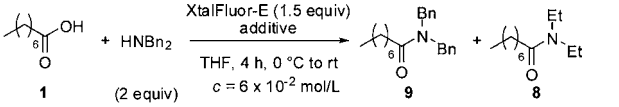


entry	amine **6**	amide (yield[a]; ee)
1	 **6a**	 **7a** (97%)
2	 **6b**	 **7b** (81%)
3	 **6c**	 **7c** (82%)
4	 **6d**	 **7d** (94%)
5	 **6e**	 **7e** (74%)
6	 **6f**	 **7f** (53%)
7	 **6g**	 **7g** (65%)
8	 **6h**	 **7h**:**7h'** = 91:9 (62%)
9[b]	 **6i**	 **7i** (74%; ee > 99%)[8]
10[c]	 **6j**	 **7j** (8%)
11	 **6k**	 **7k** (62%)
12	 **6l**	 **7l** (98%)
13	 **6m**	 **7m** (84%; ee > 99%)[8]
14	 **6n**	 **8** (89%)

[a] Isolated yields. [b] 1.1 equiv of XtalFluor-E and 5 equiv of amine were used. [c] A mixture of **7j** and **8** was obtained in a ratio **7j:8** = 13:87.

reagent, a mixture of the desired amide **9** and diethylamide **8** was obtained in a ratio of 17:83 in favor of the undesired

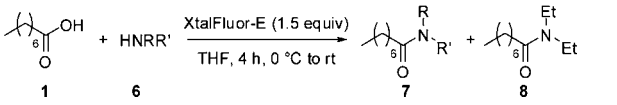
Table 4. Optimization of the Coupling Conditions

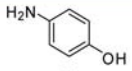


entry	$HNBn_2$ (equiv)	XtalFluor-E (equiv)	additives	ratio **9:8**[a]	yield[b] in **9**
1	2	1.5	–	17:83	–
2	2	1.5	Et_3N (3 equiv)	20:80	–
3	2	1.5	DBU (3 equiv)	20:80	–
4	**2**	**1.5**	**Proton sponge (2 equiv)**	**70:30**	**67%**
5	2	1.5	Proton sponge (3 equiv)	64:36	–
6	2	1.1	–	60:40	–
7	2	1.1	Proton sponge (2 equiv)	83:17	68%
8	**5**	**1.5**	–	**90:10**	**74%**

[a] Ratio determined by ^{1}H NMR of the crude. [b] Isolated yields.

Table 5. Amidation of Carboxylic Acids with Sterically Hindered Amines and Anilines



entry	amine **6**	ratio **7:8**[a]	amide **7** (yield)[b]
1	 **6f**	**(A)** 59:41	**7f** (53%)
		(B) 75:25	**7f** (72%)
		(C) 100:0	**7f** (77%)
2	 **6k**	**(A)** 87:13	**7k** (62%)
		(B) 88:12	**7k** (85%)
		(C) 100:0	**7k** (94%)
3	 **6o**	**(A)** 55:45	**7o** (49%)
		(B) 67:33	**7o** (67%)
		(C) 87:13	**7o** (87%)
		(D) 28:72	**7o** (21%)

[a] Ratio determined by ^{1}H NMR of the crude. [b] Isolated yields. Conditions: (**A**) 2 equiv of amine **6**, (**B**) 2 equiv of amine **6** and 2 equiv of proton sponge, (**C**) 5 equiv of amine **6**, (**D**) 2 equiv of amine **6**, $c = 6 \times 10^{-3}$ mol/L.

amide **8** (Table 4). In order to avoid deprotonation of the carboxylic acid by the valuable secondary amine (dibenzylamine), the addition of a base such as Et_3N or DBU was examined. In both cases, the ratio of **9:8** was 20:80 in favor of **8** (Table 4, entries 2–3). However, when a proton sponge such as 1,8-bis(dimethylamino)naphthalene (proton sponge) (2 equiv) was used, the ratio of **9:8** increased to 70:30 (Table 4, entry 4) and a similar ratio was obtained by addition of 3 equiv of proton sponge (64:36) (Table 4, entry 5). The use

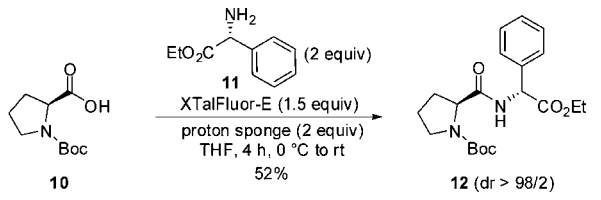
of 1.1 equiv of XtalFluor-E improved the **9:8** ratio (83:17) in favor of **9** without improvement of this yield (Table 4, entry 7). The coupling reaction between octan-1-oic acid and a large excess of dibenzylamine led to **9** in 74% yield.

The coupling reaction was also achieved between octan-1-oic acid and aniline **6f** using 2 equiv of proton sponge and 2 equiv of amine (conditions **B**), or 5 equiv of amine (conditions **C**), improving the yield in amide **7f** (Table 5, entries 1). Amides **7k** and **7o** were obtained in good yield (87−94%) even with sterically hindered secondary amines **6k** and **6o** using conditions **B** and **C** (Table 5, entries 2−3).

It is worth pointing out that realizing the reaction at 6×10^{-3} mol/L (conditions **D**) led to a mixture of amide **7o** and **8** in a ratio of 28:72 in favor of diethylamide **8**.

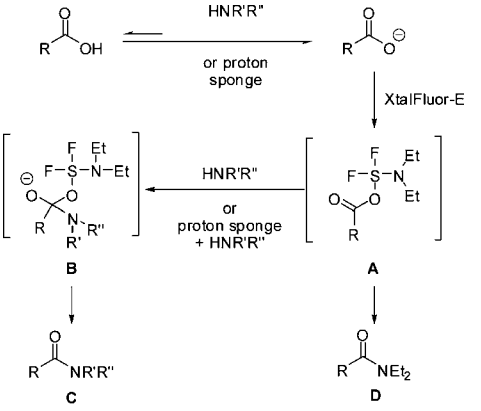
XtalFluor-E was also used in the synthesis of a dipeptide. Thus, *N*-Boc proline **10** was transformed to dipeptide **12** in 52% yield by using the optically active amine **11** with an excellent diastereomeric excess (dr > 98/2) (Scheme 1).

Scheme 1. Peptidic Coupling



From these results, it seems that different intermediates may be involved in the amidation of carboxylic acids induced by XtalFluor-E (Scheme 2). Treatment of a carboxylic acid by an amine or by a proton sponge should produce a carboxylate intermediate that can react with XtalFluor-E to produce intermediate **A**. This intermediate can be attacked intermolecularly by an amine to produce **B**, which should lead to the desired amide **C**. However, an intramolecular process can take place in intermediate **A** as the diethylamino group can attack the activated carboxylic acid to produce the undesired diethylamide **D**.[6] The latter can be the major product when the reaction is realized under high dilution. To decrease the formation of the diethylamide, either one must increase the number of equivalents of amine (5 equiv) or use a proton sponge (2 equiv) in the presence of 2 equiv of amine.

Scheme 2. Proposed Mechanism for the Formation of Amides



In conclusion, we have shown that XtalFluor-E is an efficient coupling reagent for the synthesis of amides from carboxylic acids and amines without epimerization/racemization of the substrates.

Acknowledgment. A.O. thanks Merck Serono S. A. for a grant, and Merck Serono S. A. is gratefully acknowledged for financial support.

Supporting Information Available. Experimental procedure, characterization data, and NMR spectra of compounds **3**, **5a**−**5k**, **7a**−**7o**, **8**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.