Pergamon

Tetrahedron Letters 43 (2002) 8347–8350

TETRAHEDRON LETTERS

Combined directed *ortho* metalation—intramolecular Friedel–Crafts connections. Regiospecific route to 1-substituted fluoren-9-ones

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Received 5 July 2002; revised 10 September 2002; accepted 13 September 2002

Abstract—*ortho*-Substituted-2-biphenyl carboxylic acids of the type **3a–j** were prepared by the tandem metalation sequence from 2-biphenyl carboxylic acid **1** with *sec*-butyllithium in THF at −78°C followed by quenching with electrophiles. The carboxylic acids **3a–f** were converted into 1-substituted fluorenones **4a–f** upon treatment with methanesulfonic acid.

The fluoren-9-one skeleton is found in significant classes of alkaloids, physiologically active agents, and environmental pollutants.[1] Fluorenones are also known to function as photoinitiators in various photochemical reactions.[2] The most useful syntheses of fluoren-9-ones include Friedel–Crafts closures of biarylcarboxylic acids and derivatives,[3] intramolecular [4+2] cycloaddition reactions of conjugated enynes,[4] and oxidation of fluorenes.[5] Fluoren-9-ones have been recently synthesized by palladium-catalyzed cyclization of 2-iodobenzophenones[6] and by palladium-catalyzed cyclocarbonylation of 2-halobiaryls.[7]

On the other hand, non peptidic compounds that contain a biphenyl carboxylic acid group have been shown to inhibit HIV-1 protease, with IC50 values in the range 3.4–74 μM.[8] The structure–inhibitory activity relationship demonstrates the necessity of the biphenyl carboxylic acid group for inhibition. Losartan (Merck, Sharpe & Dohme trademarks: Cozaar, Lozaar), one of the most prominent modern antihypertensive drugs, is a 2-biphenyl tetrazole derivative that, by behaving as a 'G-protein coupled receptors-needle', antagonizes the angiotensin II AT_1 receptor.[9]

In view of their tremendous importance as precursors of biologically active molecules, very little attention has been paid to the synthesis of 2-biphenyl carboxylic acid derivatives via lithiation reactions. Treatment of tertiary 2-biphenylcarboxamides and 2-biphenyloxazolines with LDA or *t*-BuLi affords the fluorenone skeleton directly by remote metalation,[10,11] alkyllithium metalation occuring exclusively *ortho* to the amide group. Unvariably, the carbonyl group is protected prior to metalation.

Regioselective lithiation of biphenyl carboxylic acids is a new challenge because of the previously demonstrated *ortho* directing effect of the carboxylic acid group in benzenoid systems.[12,13] In order to shed light on more details of the role of the carboxylic acid group in metalation, we have studied the reactivity of 2-biphenyl carboxylic acid (**1**) toward strong bases.

All the optimization reactions were carried out using commercially available 2-biphenyl carboxylic acid (**1**) under argon and THF as the solvent (Table 1). The intermediates were trapped in each case with iodomethane. The product ratio was determined by ^{1}H NMR after acidification and extraction with ether of the crude reaction mixture. Since the recovered starting acid **1** and non-acidic products were also identified in these conditions, the product distribution represents the selectivity and the efficiency of the metalation reactions. In contrast to tertiary biarylamides,[10] 2-biphenyl carboxylic acid (**1**) was unreactive toward LDA or lithium 2,2,6,6-tetramethylpiperidide (LTMP) in the interval of temperature −78→0°C in THF (entries 1–3). Treatment with *t*-BuLi (2.2 equiv.) in THF at −78°C led to the

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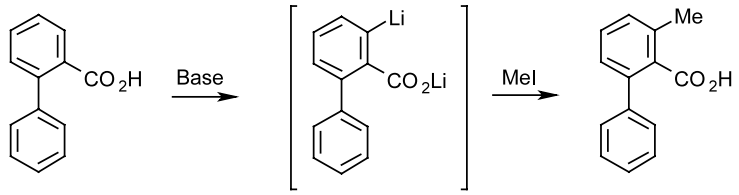
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01976-7

Table 1. Reactions of 2-biphenyl carboxylic acid (**1**) with strong bases (MeI quench) in THF

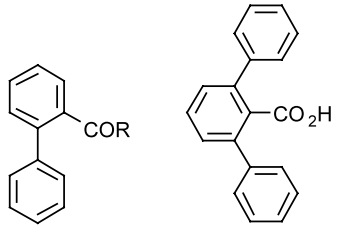


1 **2** **3a**

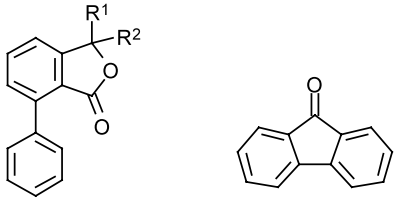
Entry	Base[a,b]	Equiv.	*T* (°C)	**1**:**3a**:**5**[c]
1	LDA	2.2	−78	100:0:0
2	LDA	3.5	0	100:0:0
3	LTMP	2.2	−78	100:0:0
4	*t*-BuLi	2.2	−78	50:50:0
5	*t*-BuLi	3.5	25	5:0:95[d]
6	*n*-BuLi	2.2	−78	20:80:0
7	*n*-BuLi/TMEDA	2.2	−78	40:60:0
8	*s*-BuLi	2.2	−78	10:90:0
9	*s*-BuLi/TMEDA	2.2	−78	65:35:0

[a] *n*-BuLi 1.6 M in hexanes. *s*-BuLi 1.3 M and 1.4 M in cyclohexane. TMEDA was distilled from CaH_2 before use. LDA and LTMP were prepared by adding *n*-BuLi (1 equiv.) to diisopropylamine (1 equiv.) and 2,2,6,6-tetramethylpiperidine (1 equiv.), respectively, in THF at −20°C.
[b] Alkyllithiums (entries 4–9): normal addition. Lithium amides (entries 1–3): reverse addition (see: Mortier, J.; Vaultier, M.; Cantegril, R.; Dellis, P. *Aldrichimica Acta* **1997**, *30*, 34). The mixture was stirred for 2 h before addition of iodomethane (4 equiv.).
[c] After acidication with 4 M HCl and extraction with ether, the molar ratio of the crude reaction mixture was determined by ^{1}H NMR.
[d] R = *t*-Bu.

ortho methylated acid **3a** albeit in moderate yield (entry 4). When 3.5 equiv. of *t*-BuLi was used at 25°C, ketone **5** was the only product identified (Table 1).



5 (R = *t*-Bu) **6**



7 R^1 = H, R^2 = OH
8 R^1 = Ph, R^2 = H

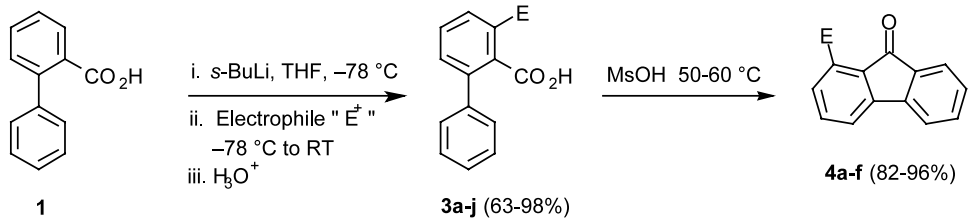
9

Acid **1** was found to be deprotonated smoothly *ortho* to the carboxylate by *n*-BuLi (2.2 equiv.) at −78°C. Quenching the orange lithium *ortho* lithiobenzoate **2** with iodomethane led to **3a** in good yield (entry 6). High conversion was achieved with *s*-BuLi at −78°C (90%, entry 8). NMR analysis of the crude reaction mixture shows that the product alkylated in *ortho* of the acid group was the only formed isomer. *N*,*N*,*N*′,*N*′-Tetramethyl-1,2-ethylenediamine (TMEDA) is known as an accelerator of metalation reactions due to its disaggregation effect on butyllithium oligomers.[14] Nevertheless, its use with either *n*-BuLi or *s*-BuLi was detrimental to the reaction, with the yield dropping from 80 and 90% to 60 and 35%, respectively (entries 7 and 9).

By employing the optimized conditions found in entry 8 with various electrophiles, acid **1** afforded the 3-substituted 2-biphenyl carboxylic acids **3a**–**j** (Table 2).[15] Methylation and ethylation of 2-biphenyl carboxylic acid **1** afforded **3a**,**b** efficiently (entries 1 and 2). Chlorination, bromination, iodination, and methylsulfenylation gave **3c**–**f** in good recrystallized yields. The smooth and high-yield reaction of chlorotrimethylsilane affording **3g** is indoubtedly related to its in situ compatibility with alkyllithiums[16] and finds further utility in regimens associated with protection of kinetically reactive anionic sites and ipso desilylation.[17] *n*-Bu_3SnCl gave **3h**, a precursor of teraryl carboxylic acid **6** via the Stille reaction (59%).[18,19] The regioselectivity of the reaction was ascertained with DMF and benzaldehyde: **3i** and **3j** underwent cyclization to hydroxyphthalide **7** and lactone **8**, respectively, upon acidic work-up.

3-Substituted 2-biphenyl carboxylic acids **3a**–**g** were then reacted with methanesulfonic acid at 50–60°C.[20] After completion of the reaction, the mixture was poured into water at 0°C and extracted with ethyl acetate. The extract was washed with water and concentrated in vacuo. Fluoren-9-ones **4a**–**f** were isolated in good yield after column chromatography (heptane/ethyl acetate). In the literature, 1-substituted fluorenones are prepared either by radical procedures[21]

Table 2. Preparation of 3-substituted 2-biphenyl carboxylic acids **3a–j** and 1-substituted fluoren-9-ones **4a–f**



Electrophile	E	Product	Yield (%)[a]	Mp (°C)	Product	Yield %[a]	Mp (°C)
MeI	Me	**3a**	80	133–134[b]	**4a**	95	98–99[f]
EtI	Et	**3b**	63	140–141	**4b**	88	93.5–94.5[g]
C_2Cl_6	Cl	**3c**	72	184–185[c]	**4c**	82	138–139[h]
$C_2Br_2Cl_4$	Br	**3d**	71	185–186	**4d**	96	132.5–133.5[i]
I_2	I	**3e**	73	169–170	**4e**	92	147–148.5[j]
Me_2S_2	MeS	**3f**	81	115–116	**4f**	91	167–168
Me_3SiCl	Me_3Si	**3g**	98	143–144	**4g**	0[k]	–
n-Bu_3SnCl	*n*-Bu_3Sn	**3h**	65	56–57	–	–	–
DMF	CHO	**3i**[d]	80	145–147	–	–	–
PhCHO	PhCH(OH)	**3j**[e]	93	91–92	–	–	–

[a] Yield of recrystallized or chromatographed (heptane/ethyl acetate) materials.
[b] Lit. mp 132°C (Carruthers W.; Poornamorthy, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2405–2409).
[c] Lit. mp 184–186°C (Hoover, J. R. E. *J. Med. Chem.* **1964**, *7*, 245–251).
[d] Not isolated but converted directly into the hydroxyphthalide **7** by acid treatment upon work-up.
[e] Not isolated but converted directly into the lactone **8** by acid treatment upon work-up.
[f] Lit. mp 97–98°C (Lothrop, W. C.; Goodwin, P. A. *J. Am. Chem. Soc.* **1943**, *65*, 363).
[g] Lit. mp 91–93°C (Tomioka, H; Kawasaki, H.; Kobayashi, N.; Hirai, K. *J. Am. Chem. Soc.* **1995**, *117*, 4483–4498).
[h] Lit. mp 137–138°C (Huntress, E. H.; Pfister, K.; Pfister, K. H. T. *J. Am. Chem. Soc.* **1942**, *64*, 2845–2849).
[i] Lit. mp 134–134.5°C (Huntress, E. H.; Pfister, K.; Pfister, K. H. T. *J. Am. Chem. Soc.* **1942**, *64*, 2845–2849).
[j] Lit. mp 144–145°C (Huntress, E. H.; Pfister, K.; Pfister, K. H. T. *J. Am. Chem. Soc.* **1942**, *64*, 2845–2849).
[k] Fluorenone **9** was formed exclusively.

or by palladium(0)-catalyzed cross-coupling reactions of aryl bromides/triflates with arylboranes.[11] The direct *ortho* lithiation of the aminoalkoxide derived from parent fluorenone has also been reported.[22] The Si and Sn groups were not resistant to the acidic conditions used and the parent fluorenone **9** was formed in both cases.

The fluoren-9-one skeleton can also be obtained from the corresponding 2-biphenyl carboxylic acids by a process involving the 'superbasic' *n*-butyllithium/*t*-BuOK mixture (the Schlosser base). This work will be reported elsewhere.

Acknowledgements

This work was supported by the CNRS, Université du Maine and Institut universitaire de France.

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15. The preparation of **3a** is representative: at −78°C, *s*-BuLi (1.3 M in cyclohexane, 2.2 equiv., 55.4 mmol, 42.6 mL) was added dropwise—over a period of 30 min—to a vigorously stirred solution of 2-biphenyl carboxylic acid (**1**) (25.2 mmol, 5.0 g) in THF (180 mL) under an argon atmosphere. After 2.5 h at −78°C, the mixture was treated with iodomethane (75.6 mmol, 4.7 mL) in THF (40 mL). The resulting solution was allowed to warm up to ambient temperature, after which water was added. The aqueous layer was washed with diethyl ether, and shaken, and then acidified with 4 M HCl. The mixture was diluted with diethyl ether and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo followed by recrystallization (heptane–ethylacetate) gave **3a** as white crystals (4.30 g, 80%). Mp 133–134°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.5 (1H, br, s), 7.39–7.32 (6H, m), 7.20 (1H, d, $J=2$ Hz), 7.19 (1H, d, $J=2.4$ Hz), 2.43 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.43, 139.91, 134.66, 131.43, 128.92, 128.42, 127.70, 127.56, 126.74, 126.40, 19.10 (CH_3). Anal. calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.44; H, 5.72%.
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