Pergamon

Tetrahedron Letters 42 (2001) 1115–1118

TETRAHEDRON LETTERS

Direct release of nitriles from solid phase

Neal D. Hone,[a,*] Lloyd J. Payne[a] and Colin M. Tice[b]

[a]*Cambridge Discovery Chemistry, The Merrifield Centre, Rosemary Lane, Cambridge CB1 3LQ, UK*
[b]*Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477-0904, USA*

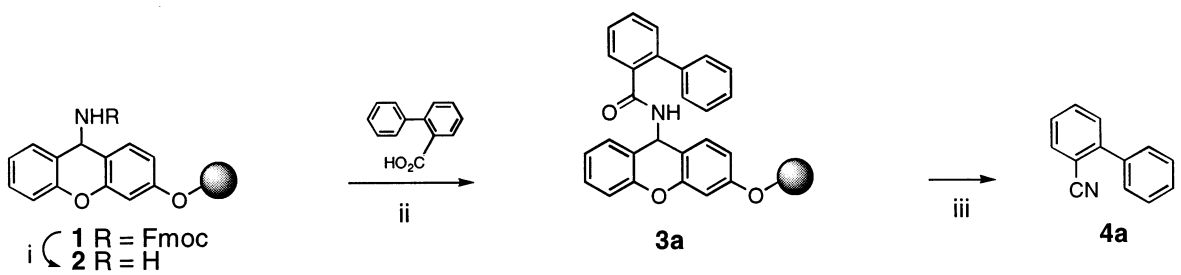
Received 15 August 2000; revised 27 October 2000; accepted 8 November 2000

Abstract—Cleavage conditions are described which allow resin bound secondary amides to be liberated from Sieber or Rink resin as nitriles. The method has been applied to the synthesis of a series of cyanobiaryls. © 2001 Published by Elsevier Science Ltd.

Solid phase organic synthesis (SPOS) has its roots in peptide chemistry.[1] The widespread adoption of SPOS for the generation of libraries of small molecules for drug and agrochemical discovery has led to the development of a variety of linkers that allow the release of a range of functional groups beyond that typical of peptides.[2] The traceless linkers developed by several groups are particularly noteworthy in this context.[3] In this letter we report conditions that allow the direct release of nitriles from Sieber and Rink resins[4] in excellent yields. Nitriles are found in a number of biologically active molecules ranging from pyrethroid insecticides, e.g. fenvalerate to the cardiotonic milrinone. Thus, this method adds a significant new method to the SPOS toolbox.[5] As a demonstration of its utility we have prepared a series of cyanobiaryls.

Fmoc Sieber resin **1** was deprotected under standard conditions to give **2** and biphenyl-2-carboxylic acid was coupled under standard conditions[6] to afford resin bound amide **3a** (Scheme 1). Amide **3a** was treated with trifluoroacetic anhydride (TFAA, 5 equiv.) and pyridine (10 equiv.) in dichloromethane at room temperature overnight to furnish a crude product containing the desired 2-cyanobiphenyl **4a** in addition to by-products derived from TFAA and pyridine (Method A).[7] A simple aqueous work up afforded **4a** in 82% yield (Table 1, Entry 1). Treatment of seven additional resin bound amides **3b–h** with TFAA/pyridine afforded the expected nitriles **4b–h** in 51–98% yield (Table 1, Entries 2–8).

Further exploration of this chemistry revealed that cleavage of **3a** to **4a** can also be effected using trichloroacetyl chloride and triethylamine (Method B) or with Burgess reagent (methoxycarbonyl sulfamoyl) triethylammonium hydroxide, inner salt (Method C) albeit in lower yields (Table 1: Entry 1 versus 2 and 3; Entry 5 versus 6 and 7). In addition, Rink resin can also be employed in place of Sieber resin with equal or



Scheme 1. (i) 20% piperidine in DMF, rt, 30 min; (ii) TBTU, HOBt, DIEA, DMF, rt, 2 h; (iii) TFAA (5 equiv.), pyridine (10 equiv.), DCM, rt, 12 h.

Keywords: solid phase synthesis; combinatorial chemistry; libraries; nitriles; biphenyls.
* Corresponding author.

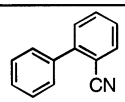
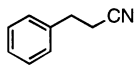
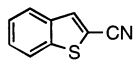
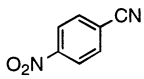
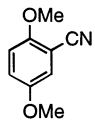
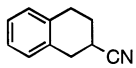
0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01988-2

better product yields but slightly reduced purities. (Table 1: Entry 1 versus 4; Entry 5 versus 8).

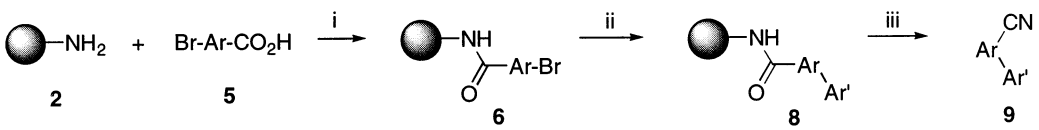
The facile dehydration of Sieber and Rink amides is in contrast to the more forcing conditions usually required for secondary amides. The electron rich nature of these benzylamides presumably enhances both the nucleophilicity of the amide during *O*-trifluoroacetylation as well as benzylic cleavage prior to TFA elimination. The corresponding amides formed from aminomethyl polystyrene are stable to the cleavage/dehydration conditions. Certain functional groups such as primary and secondary amines, primary amides and alcohols are expected to be incompatible with these conditions.

As a demonstration of the utility of the method, we combined it with the solid phase Suzuki reaction[8] allowing synthesis of a series of cyanobiaryls (Scheme 2). Several groups have recognised the utility of the biphenyl scaffold and employed it in library synthesis.[9] Bromoarylcarboxylic acids **5a**–**h** were coupled to Sieber resin **2** using standard conditions to afford resin bound amides **6a**–**h**.[5] Bromine analyses of **6a**–**h** indicated that the loading reaction had been successful. Suzuki couplings with various benzeneboronic acids **7** (Table 2) were carried out under the conditions of Frenette and Friesen[8b] to afford resin bound biarylamides **8**. Cleavage from the resin using TFAA/pyridine (Method A) afforded the crude cyanobiaryls **9**. By-products from the cleavage cocktail could be removed either by aqueous workup (ether/saturated aqueous sodium bicarbonate) or by solid supported liquid extraction (SLE)[10] to provide the expected cyanobiaryls **9**, generally in good yield and purity (Table 2).

Table 1. Nitriles synthesised on solid phase

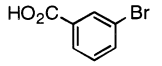
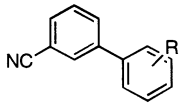
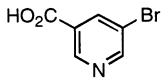
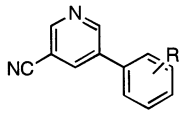
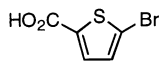
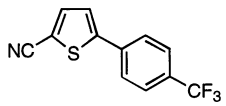
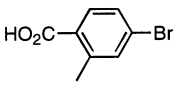
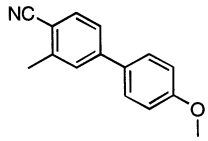
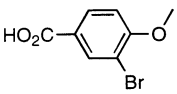
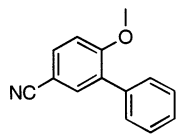
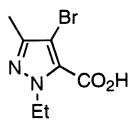
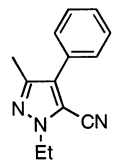
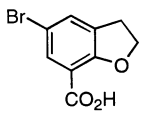
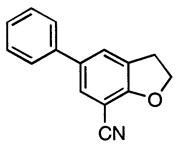
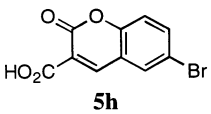
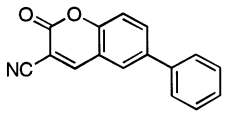
Entry	Resin **2**	Cleavage Method[a]		Nitrile[b]	Purity[c] (%)	Yield[d] (%)
1	Sieber	A	**4a**		99	82
2	Sieber	B				64[e]
3	Sieber	C				18[e]
4	Rink	A			94	100
5	Sieber	A	**4b**		98	98
6	Sieber	B				74[e]
7	Sieber	C				86[e]
8	Rink	A			95	100
9	Sieber	A	**4c**		99	51
10	Sieber	A	**4d**		98	98
11	Sieber	A	**4e**		91	60
12	Sieber	A	**4f**	Fmoc-NHCH(Me)CN	94	50
13	Sieber	A	**4g**	Boc-NHCH(Me)CN	75	86
14	Sieber	A	**4h**		95	93

a. Method A: TFAA (5 eq), pyridine (10 eq), CH_2Cl_2, rt, 16 h; Method B: Cl_3CCOCl (5 eq), Et_3N (5.5 eq), CH_2Cl_2, rt, 16 h; Method C: Burgess reagent (3 eq), THF, reflux, 16 h. b. All products gave satisfactory ^{1}H-NMR, IR and mass spectral data. c. Purity was determined by HPLC. d. Yields were calculated based on the initial functionalisation of the polymeric support. e. Crude product was purified by column chromatography.



Scheme 2. (i) TBTU, HOBt, DIEA, DMF, rt, 18 h; (ii) Ar′B(OH)$_2$ (**7**), Pd(PPh$_3$)$_4$, Na_2CO_3, DME, Δ, 48 h; (iii) TFAA (5 equiv.), pyridine (10 equiv.), DCM, rt, 16 h.

Table 2. Cyanobiaryls synthesised

Br-Ar-CO_2H	Ar'$B(OH)_2$	Cyanobiaryl[a]		Purity[b] (%)	Yield[c] (%)
 **5a**	**7a** 4-$MeOC_6H_4B(OH)_2$		**9aa** R = 4-MeO	91[d]	78
	7b 4-$MeC_6H_4B(OH)_2$		**9ab** R = 4-Me	92	86
	7c 2-$CF_3C_6H_4B(OH)_2$		**9ac** R = 2-CF_3	91[e]	80
 **5b**	**7d** $PhB(OH)_2$		**9bd**	99[d]	62
 **5c**	**7e** 4-$CF_3C_6H_4B(OH)_2$		**9ce**	92[d]	71
 **5d**	**7a** 4-$MeOC_6H_4B(OH)_2$		**9da**	85[d]	89
 **5e**	**7d** $PhB(OH)_2$		**9ed**	97[d]	67
 **5f**	**7d** $PhB(OH)_2$		**9fd**	97[d]	80
 **5g**	**7d** $PhB(OH)_2$		**9gd**	95[e]	82
 **5h**	**7d** $PhB(OH)_2$		**9hd**	25[ef]	52

a. All compounds gave satisfactory ^{1}H-NMR and MS spectra. b. Purity was determined by GC (HP1 column, FID). c. Yields were calculated based on the initial functionalisation of the polymeric support. d. Aqueous workup (ether/saturated aq $NaHCO_3$). e. SLE[10] f. An unidentified compound was the major product.

In conclusion, we have developed a practical solid phase synthesis of nitriles and demonstrated its utility by preparing a number of cyanobiaryls.

References

1. (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154. (b) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *50*, 8135–8173. (c) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385–15443. (d) Loughlin, W. A. *Aust. J. Chem.* **1998**, *51*, 875–893.
2. James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946.
3. (a) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999–12000. (b) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498–6499. (c) Hughes, I. *Tetrahedron Lett.* **1996**, *37*, 7595–7598. (d) Hone, N. D.; Davies, S. G.; Devereux, N. J.; Taylor, S. L.; Baxter, A. D. *Tetrahedron Lett.* **1998**, *39*, 897–900.
4. Novabiochem Rink Amide MBHA (1% DVB crosslinked, 0.59 mmol/g) and Sieber Amide (1% DVB crosslinked, 0.6 mmol/g) resins were employed.
5. A method for conversion of ketones $R^1C(=O)R^2$ to the corresponding nitrile $R^1CH(C\equiv N)R^2$ via a polymeric phenylsulfonylhydrazone has been reported: Kamogawa, H.; Kanzawa, A.; Kadoya, M.; Naito, T.; Nanasawa, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 762–765.
6. (a) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927–1930. (b) Matsoukas, J. M.; Panagiotopoulos, D.; Keramida, M.; Mavromoustakos, T.; Yamdagni, R.; Wu, Q.; Moore, G. J.; Saifed-

dine, M.; Hollenberg, M. D. *J. Med. Chem.* **1996**, *39*, 3585–3591.
7. Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813–1816.
8. (a) Lorsbach, B. A.; Kurth, M. J. *Chem Rev.* **1999**, *99*, 1549–1581. (b) Frenette, R.; Friesen, F. W. *Tetrahedron Lett.* **1994**, *35*, 9177–9180.
9. (a) Neustadt, B. R.; Smith, E. M.; Lindo, N.; Nechuta, T.; Bronnenkant, A.; Wu, A.; Armstrong, L.; Kumar, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2395–2398. (b) Pavia, M. R.; Cohen, M. P.; Dilley, M. J.; Dubuc, G. R.; Durgin, T. L.; Forman, F. W.; Hediger, M. E.; Milot, G.; Powers, T. S.; Sucholeiki, I.; Zhou, S.; Hangauer, D. G.; *Bioorg. Med. Chem.* **1996**, *4*, 659–666.
10. Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097–4106.