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Preparation of *N*-hydroxysuccinimido esters via palladium-catalyzed carbonylation of aryl triflates and halides☆

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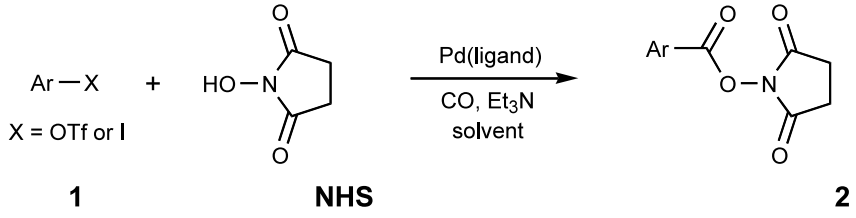
Abstract—*N*-Hydroxysuccinimido esters of aromatic carboxylic acids (a.k.a. active esters) can be made using a potentially general, one-step procedure via Pd-catalyzed carbonylation of an aryl triflate or aryl iodide with CO and *N*-hydroxysuccinimide. Excellent yields (up to 94%) were observed when the reaction was done in DMSO at 70°C and 1 atmosphere of CO pressure.

Carboxylic acid esters of *N*-hydroxysuccinimide (NHS) have been widely used in organic synthesis as reactive acylating reagents (a.k.a. active esters). These active esters are especially useful as intermediates in the synthesis of peptides and proteins via *N*-acylation.[2] In addition, a number of biologically important molecules such as receptor antagonists,[3] nucleotides[4] and labeling reagents[5] have been chemically modified using *N*-hydroxysuccinimido ester intermediates. More recently, *N*-hydroxysuccinimido esters have been used to acylate other nucleophiles such as alcohols[6] and a hydroxylamine.[7] Thorough investigations (e.g., mechanism, scope, preparation) on the chemistry of *N*-hydroxysuccinimido esters have been reported.[8,9]

The classical method for making *N*-hydroxysuccinimido esters involves the reaction of the sodium, potassium, silver or thallium salt of NHS with an acyl chloride.[10] Other common methods of preparation involve esterifying a carboxylic acid with NHS in the presence of dicyclohexylcarbodiimide[11] or azodicarboxylate/triphenylphosphine.[12] The reaction of bis(*N*-succinimidyl) carbonate with carboxylic acids also affords the corresponding active esters in high yield.[13] Additionally, acylation of NHS with mixed anhydrides has been used.[14]

However, these methods are limited in their utility if the required carboxylate is not readily available. Therefore, we envisioned a process (Scheme 1) whereby an *N*-hydroxysuccinimido ester **2** could be made in one-step from readily available starting materials, namely aryl triflates or halides (**1**). Specifically, we wanted to apply known Pd-catalyzed carbonylation chemistries in a novel way by reacting the aryl triflate (or halide) with CO and NHS. Several reports have appeared where aryl triflates and halides have been converted to aryl amides and esters,[15,16] however, to our knowledge, we have not seen this process used to make active esters. This new method would be very useful in, for example,



Scheme 1.

Keywords: Pd-catalyzed carbonylation; active ester; *N*-hydroxysuccinimide.

☆ A preliminary account of this work has appeared, see Ref. 1.

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the synthesis of series of aryl carboxamide derivatives from a common carboxylate-containing core intermediate. We now wish to describe this novel and convenient method (Scheme 1) for the preparation of *N*-hydroxysuccinimido esters **2** of aromatic carboxylic acids directly from aryl triflates or aryl iodides under Pd-catalyzed carbonylation conditions.

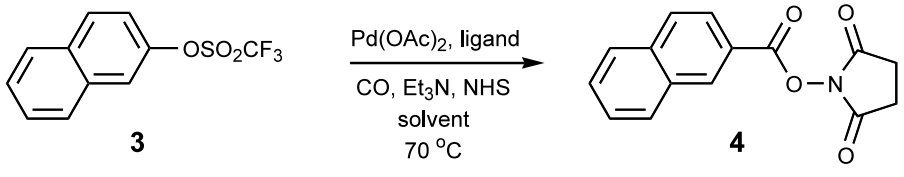
The triflate ester **3**[17] of 2-naphthol was used as substrate to optimize conditions. As shown in Scheme 2, we varied the Pd ligand (Xantphos, DPPF, DPPP, BINAP, DCPE, and PPh_3),[18] solvent (DMSO, DMF, toluene and dioxane), and stoichiometry while keeping Pd source [$Pd(OAc)_2$], base (Et_3N), temperature (70°C), and pressure (1 atmosphere CO) constant. For the conversion of **3** to the corresponding active ester **4**, we observed that an excellent yield of 94% could be realized using Xantphos[19] (5 mol%) as Pd ligand with a 1:1.4:1.5 molar ratio of **3**:NHS:Et_3N in DMSO for 17 h.[20]

When Xantphos was replaced with the following well-known Pd ligands, lower yields for this conversion were realized: BINAP (32%), DPPF (40%), DPPP (72%), PPh_3 (no reaction up to 10 mol%) or DCPE (no reaction up to 10 mol%). With the exception of dioxane, yields were considerably lower when DMSO was replaced with the following solvents known to be useful in Pd catalyzed reactions: DMF (59%), dioxane (90%), THF (63%), and toluene (61%). The ability of DMSO to accelerate Pd-catalyzed carbonylation reactions has been previously reported[21] and sulfoxides are known to form a strong complex with Pd(II).[22] The amount of Pd ligand and molar ratio of **3**:NHS:Et_3N, are also important determinants to the success of the reaction. For example, when 2.5 mol% Xanthpos was used versus the 5 mol% in the optimized conditions,[20] the yield of product decreased from 94 to 80%. Likewise, when the ratio of **3**:NHS:Et_3N was varied from the optimized 1:1.4:1.5 ratio to, for example, 1:1.05:1.2, 1:1.4:3.0 and 1:2.5:1.5, the yields decreased to 87, 74, and 51%, respectively. Lastly, the success of this reaction was not highly dependent on time, in that TLC showed little starting material after 5 h and little or no product decomposition after 24 h.

Using these optimized conditions,[20] we studied the potential generality of the reaction by varying the nature of the aromatic group (Ar) and leaving group (X) of the substrate. Substrates were selected based on diversity of physicochemical properties and, coincidentally, most substrates and many products are known. Results are summarized in Table 1. Using X = OTf and the optimized conditions identified for Ar = 2-naphthyl (entry 1),[20] we found that many triflates reacted with carbon monoxide and NHS smoothly to give rise to the corresponding esters in very good yields. For example, variation of the aromatic core to 1-naphthyl or phenyl provided the corresponding active esters in 88 and 72% yields, respectively (entries 2 and 3). However, when the 3-pyridinyl analogue was used in the reaction (entry 4), no desired product was obtained with the only isolable material being 3-pyridinol which we believe results from cleavage of the triflate ester by NHS.

When the phenyl substrate were substituted with alkyl groups (entries 5–9), very good yields were observed (66–91%) with the exception of 2-tolyl (entry 7). Here, the lower yield observed (47%) may be a consequence of steric congestion in the intermediates or transition states of the reaction, however, the 1-naphthyl case (entry 2) gives an excellent result and contradicts this steric argument. When the phenyl ring was substituted with heteroatom-containing groups, variable results were observed. When the 4-MeO-C_6H_4 substrate (entry 10) was used, a moderate yield of 57% was obtained. When electron-withdrawing substituents such as 4-NO_2 or 4-Cl were used (entries 11 and 12, respectively), however, no product was observed. As was seen with the 3-pyridinyl substrate (entry 4), only the corresponding phenols were evident. However, when the 4-Cl was combined with a 3-methyl group (entry 13), an 84% yield was realized. It is apparent that when substrates contain electron-withdrawing groups (entries 4, 11 and 12), cleavage of the triflate ester by a nucleophile which we assume is NHS, competes with carbonylation due to the excellent leaving group abilities of these phenols. Sulfur–oxygen bond cleavage in the reaction of aryl fluoroalkanesulfonate with nucleophiles has been reported previously.[23]

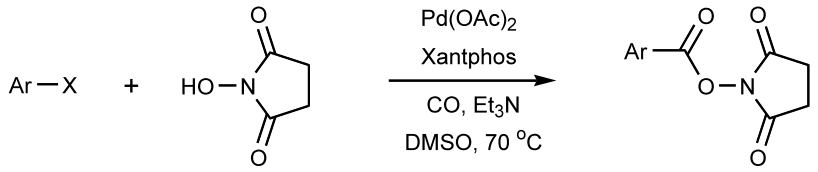
We also studied the effect of variation of the leaving group by evaluating iodobenzene (entry 14), bromobenzene (entry 23) and chlorobenzene (entry 24) as substrates in the reaction. Replacing the triflate of PhOTf with iodo has a positive effect with the yield increasing from 72% (entry 3) to 86% (entry 14). However, using bromine (entry 23) and chlorine (entry 24) as leaving groups significantly reduced yields (26% and no product detectable, respectively). When a variety of functional groups where introduced into iodobenzene, all substrates evaluated (entries 15–22) gave very good results with many yields above 90%. In contrast to the phenyl triflates shown in entries 3, 11 and 12, introduction of electron-withdrawing groups into iodobenzene is not detrimental (entries 16–18) to the success of the reaction. Here, of course, there is no competing triflate



3 4

Scheme 2.

Table 1. Preparation of *N*-hydroxysuccinimide esters via Pd-catalyzed carbonylation of aryl triflates and aryl halides[a]



Entry	Ar	X	Yield (%)[b]
1[c]	2-Naphthyl	OTf	94
2[d]	1-Naphthyl	OTf	88
3[e]	C_6H_5	OTf	72
4[e]	3-Pyridinyl	OTf	ND[f]
5[g]	4-Me-C_6H_4	OTf	66
6[e]	3-Me-C_6H_4	OTf	88
7[h]	2-Me-C_6H_4	OTf	47
8[i]	3,4-Me_2-C_6H_3	OTf	93
9[i]	5,6,7,8-H_4-2-Naphthyl	OTf	91
10[e]	4-MeO-C_6H_4	OTf	57
11[e]	4-NO_2-C_6H_4	OTf	ND[f]
12[e]	4-Cl-C_6H_4	OTf	ND[f]
13[i]	4-Cl-3-Me-C_6H_3	OTf	84
14[e]	C_6H_5	I	86
15[e]	4-MeO-C_6H_4	I	85
16[e]	4-NO_2-C_6H_4	I	73
17[j]	4-CN-C_6H_4	I	93
18[e]	4-Cl-C_6H_4	I	90
19[e]	2-Me-C_6H_4	I	92
20[i]	4-MeO-3-MeOCO-C_6H_3	I	72
21[e]	3-Pyridinyl	I	61
22[e]	2-Thienyl	I	83
23[e]	C_6H_5	Br	26
24	C_6H_5	Cl	ND[k]

[a] See Ref. 20.
[b] Refers to isolated yields after purification by flash column chromatography. Spectroscopic data (IR, ^{1}H NMR, MS) were in agreement with the assigned structures.
[c] See Ref. 25 for alternative preparation of product.
[d] See Ref. 26 for alternative preparation of product.
[e] Product is commercially available.
[f] Product formation Not Detectable (ND); only the corresponding phenol was observed in the reaction mixture.
[g] See Ref. 27 for alternative preparation of product.
[h] See Ref. 9 for alternative preparation of product.
[i] New compounds gave satisfactory element analysis.
[j] See Ref. 28 for alternative preparation of product.
[k] Product formation Not Detectable (ND); only decomposition to unidentified by-products was observed.

cleavage reaction possible. Relative to the corresponding triflates or bromides, we observed that aryl iodides underwent the Pd-catalyzed carbonylation faster and in higher yields regardless of the presence of electron-withdrawing or -donating groups on aromatic rings.

In conclusion, we have found that readily available aryl triflates and aryl iodides can be converted to the corresponding *N*-hydroxysuccinimido activated esters in high yields using common and inexpensive reagents under Pd-catalysis. With respect to the leaving group, the yield and rate of the reaction follows the rank order: Aryl iodide > aryl triflate > aryl bromide > aryl chloride. This is in agreement with reported rates of the oxidative addition process of C–X (X = halo or CF_3SO_3) to the palladium(0) complex.[24] A variety of functional groups on the aromatic ring of the substrate including alkyl, Cl, NO_2, CN, MeO, and MeOCO are tolerated by the reaction conditions used to make these active esters. The reaction appears to be tolerant to steric effects imparted by either *ortho* substitution or 1,8-*peri* interactions. Heteroaromatic substrates such as 3-pyridinyl and 2-thienyl can be successfully used when the substrate is an aryl iodide. This new method offers an attractive and potentially general alternative to make *N*-succinimidyl esters of aromatic carboxylic acids to the more standard procedures starting with aromatic carboxylic acids or acid halides. Further investigations to expand the scope and utility of this and related reactions are currently underway.

Acknowledgements

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References

1. Lou, R.; VanAlstine, M. A.; Wentland, M. P. Abstracts of the 224th American Chemical Society National Meeting, Boston, MA, August 18–22, 2002, ORGN 456.
2. (a) Hypolite, C. L.; McLernon, T. L.; Adams, D. N.; Chapman, K. C.; Herbert, C. B.; Huang, C. C.; Distefano, M. D.; Hu, W. *Bioconjugate Chem*. **1997**, *8*, 658–663; (b) Sagawa, T.; Ishida, H.; Urabe, K.; Yoshinaga, K.; Ohkubo, K. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1–5; (c) Mackiewicz, Z.; Belisle, S.; Bellabarba, D.; Gallo-Payet, N.; Lehoux, J.; Lagace, G.; Esher, E. *Helv. Chim. Acta* **1987**, *70*, 423–429; (d) Akiyama, M.; Shimizu, K.; Narita, M. *Tetrahedron Lett*. **1976**, 1015–1018; (e) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc*. **1964**, *86*, 1839–1842.
3. (a) Rosini, M.; Budriesi, R.; Bixel, M. G.; Bolognesi, M. L.; Chiarini, A.; Hucho, F.; Krogsgaard-Larsen, P.; Mellor, I. R.; Minarini, A.; Tumiatti, V.; Usherwood, P. N. R.; Melchiorre, C. *J. Med. Chem*. **1999**, *42*, 5212–5223; (b) Sivvas, E.; Voukelatou, G.; Kouvelas, E. D.; Francis, G. W.; Aksnes, D. W. *Acta Chem. Scand*. **1994**, *48*, 76–79.
4. (a) Sengle, G.; Jenne, A.; Arora, P. S.; Seelig, B.; Nowick, J. S.; Jaschke, A.; Famulok, M. *Bioorg. Med. Chem*. **2000**, *8*, 1317–1329; (b) Kolpashchikov, D. M.; Ivanova, T. M.; Boghachev, V. S.; Nasheuer, H.-P.; Weisshart, K.; Favre, A.; Pestryakov, P. E.; Lavrik, O. I. *Bioconjugate Chem*. **2000**, *11*, 445–451.
5. (a) Adamczyk, M.; Fishpaugh, J. R.; Mattingly, P. G. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 217–220; (b) Mayer, T. G.; Weingart, R.; Munstermann, F.; Kawada, T.; Kurzchalia, T.; Schmidt, R. R. *Eur. J. Org. Chem*. **1999**, *10*, 2563–2571; (c) Tenetova, E. D.; Dobrikov, M. I.; Shishkin, G. V.; Shteingartz, V. D. *Russ. Chem. Bull*. **1998**, *47*, 321–326; (d) Henriksen, U.; Buchardt, O. *Tetrahedron Lett*. **1990**, *31*, 2443–2444; (e) Dupuis, G. *Can. J. Chem*. **1987**, *65*, 2450–2453; (f) Keana, J. F. W.; Ogan, M. D.; Lu, Y.; Beer, M.; Varkey, J. *J. Am. Chem. Soc*. **1986**, *108*, 7957–7963.
6. Turnbull, K.; Beladakere, R. N.; McCall, N. D. *J. Heterocyclic Chem*. **2000**, *37*, 383–388.
7. Bark, S. J.; Schmid, S.; Hahn, K. M. *J. Am. Chem. Soc*. **2000**, *122*, 3567–3573.
8. Cline, G. W.; Hanna, S. B. *J. Am. Chem. Soc*. **1987**, *109*, 3087–3091.
9. Hirata, H.; Higuchi, K.; Yamashina, T.; Sugiura, M. *Yukagaku* **1991**, *40*, 1088–1094.
10. (a) Neunhoeffer, O.; Gottschlich, R. *Justus Liebigs Ann. Chem*. **1970**, *736*, 100–109; (b) Bauer, L.; Miarka, S. V. *J. Am. Chem. Soc*. **1957**, *79*, 1983–1985; (c) Paquet, A. *Can. J. Chem*. **1976**, *54*, 733–737.
11. Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc*. **1964**, *86*, 1839–1842.
12. Grochowski, E.; Jurczak, J. *Synthesis* **1977**, 277–279.
13. Parameswaran, K. N. *Org. Prep. Proced. Int*. **1990**, *22*, 119–121.
14. Anderson, G. W.; Callahan, F. M.; Zimmerman, J. E. *J. Am. Chem. Soc*. **1967**, *89*, 178.
15. Reviews: (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*, Plenum Press: New York, 1991; (b) Malleron, J. L.; Fiaud, J. C.; Legros, J. Y. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, 1997; p. 250; (c) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A: Chem*. **1995**, *104*, 17–85.
16. (a) Wentland, M. P.; Lou, R.; Ye, Y.; Cohen, D. J.; Richardson, G. P.; Bidlack, J. M. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 623–626; (b) Wentland, M. P.; Lou, R.; Dehnhardt, C. M.; Duan, W.; Cohen, D. J.; Bidlack, J. M. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1717–1721.
17. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc*. **1987**, *109*, 5478–5486.
18. Xantphos: 4,5-Bis(diphenylphosphino)-9,9′-dimethylxanthene. DPPF: 1,1′-bis(diphenylphosphino)ferrocene. DPPP: 1,3-Bis(diphenylphosphino)propane. BINAP: rac-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. DCPE: 1,2-Bis(dicyclohexylphosphino)ethane.
19. (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *4*, 3081–3089; (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 6043–6048.
20. Procedure used to *N*-hydroxysuccinimidyl 2-naphthoate (Table 1, entry 1): DMSO and triethylamine were degassed by the way of three freeze–thaw cycles and *N*-hydroxysuccinimide was dried over P_2O_5 in vacuum for 24 h. Under argon atmosphere, triethylamine (0.31 mL, 2.25 mmol) was added to a mixture of 2-naphthyl triflate (414.0 mg, 1.5 mmol), palladium acetate (16.8 mg. 0.075 mmol), Xantphos (43.4 mg, 0.075 mmol) and *N*-hydroxysuccinimide (241.5 mg, 2.1 mmol) in DMSO (2 mL). The solution was purged with carbon monoxide for 15 min and stirred under a CO balloon at 70°C for 17 h. The reaction mixture was then cooled to room temperature, diluted with 20 mL of ethyl acetate and washed with saturated sodium bicarbonate solution and water. The organic phase was dried over sodium sulfate and evaporated to give crude product. Chromatography on silica gel using hexane:acetone (4:1) provided 381.3 mg (94%) *N*-hydroxysuccinimidyl 2-naphthoate as a white crystalline solid.
21. Cacchi, S.; Lupi, A. *Tetrahedron Lett*. **1992**, *33*, 3939–3942.
22. Bancroft, D. P.; Cotton, F. A.; Verbruggen, M. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun*. **1989**, *C45*, 1289–1292.
23. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett*. **1986**, *27*, 3931–3934.
24. (a) Beller, M.; Cornils, B.; Fohrning, C. D.; Kohlpainter, C. W. *J. Mol. Catal*. **1995**, *104*, 17; (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1895.
25. Doughty, M. B.; Chaurasia, C. S.; Li, K. *J. Med. Chem*. **1993**, *36*, 272–279.
26. Shiosaki, K.; Nadzan, A. M.; Garvey, D. S.; Shue, Y.-K.; Brodie, M. S.; Holladay, M. W.; Chung, J. Y.-L.; Tufano, M. D.; May, P. D. US Patent 1994, 5340802.
27. Pochlauer, P.; Hendel, W. *Tetrahedron* **1998**, *54*, 3489–3494.
28. Iijima, K.; Katada, J.; Yasuda, E.; Uno, I.; Hayashi, Y. *J. Med. Chem*. **1999**, *42*, 312–323.