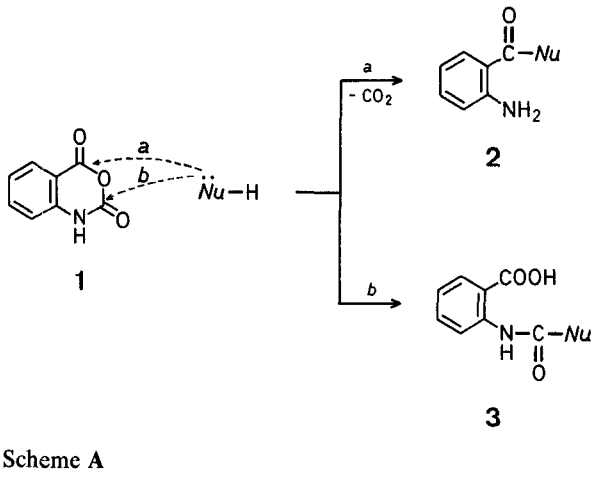
Active Esters of Anthranilic Acid; *N*-(*o*-Aminobenzoyloxy)-imides as Reagents for *o*-Aminobenzoylation

Charles HINMAN, Keith VAUGHAN*

Department of Chemistry, Saint Mary's University, Halifax, Nova Scotia, Canada, B3H 3C3

Anthranilamides **7** have been used as precursors for the synthesis of a variety of nitrogen-containing heterocycles, e.g. quinazolinones[1], benzothiadiazinones[2], benzotriazinones[3], benzodiazepinediones[4], benzodiazaphosphorins[5], and quinazolinobenzotriazinones[6]. The preparation of anthranilamides by *o*-aminobenzoylation of amines is limited by the availability of reagents for *o*-aminobenzoylation; conventional methods of aroylation via the aroyl halide or anhydride are not possible. The most frequently used reagent for this purpose is isatoic anhydride (2*H*-3,1-benzoxazin-2,4(1*H*)-dione; **1**), which reacts readily with some amines by attack at C-4 and displacement of carbon dioxide to afford the anthranilamide[7] **2** (Scheme **A**, path *a*). A competing pathway *(b)* in these reactions is attack at C-2 of **1** giving rise to urea derivatives **3**. Urea formation may be predominant in reactions of **1** with sterically hindered nucleophiles, sometimes with total exclusion of anthranilamide formation[8] unless solvents such as dimethylformamide or dimethyl sulfoxide are employed[9].

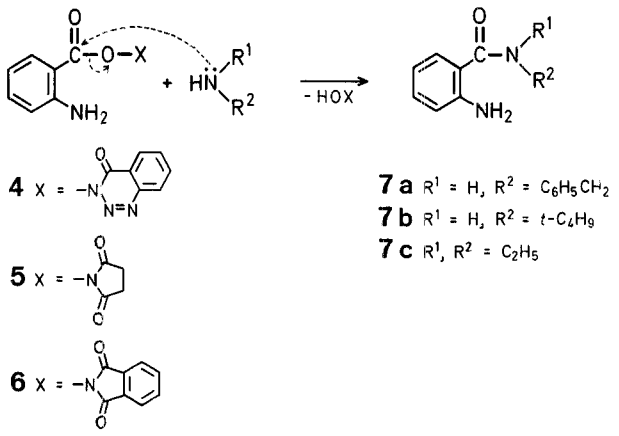


Scheme **A**

In a previous report[10], the novel heterocyclic triazine **4** was found to be an *o*-aminobenzoylating agent in reactions with benzylamine. This observation has led to a search for structurally similar *o*-aminobenzoyloxy-heterocycles, such as the *o*-aminobenzoyloxysuccinimide (**5**). The latter active ester has been described as a reagent for fluorescence labelling of enzymes[11] but its properties and potential application have not been fully explored. This communication reports the synthesis and characterisation of the active ester **5**, and of the phthalimide analogue **6**, and an investigation of their reaction with some nucleophilic amines (Scheme **B**).

N-(*o*-Aminobenzoyloxy)-succinimide (**5**) was prepared by condensation of anthranilic acid and *N*-hydroxysuccinimide in dioxan in the presence of dicyclohexylcarbodiimide[12]; 4-dimethylaminopyridine was used as an acylation catalyst[13] which increased the yield moderately. The active ester solution obtained in this way could be used immediately for reaction with the nucleophile (*in situ*, Method A).

0039-7881/80/0932-0719 $ 03.00



Scheme B

Alternatively, purification of the solution afforded the crystalline active ester **5**, which crystallises from *n*-propanol and appears to be quite stable. Some deterioration (possibly photolytic decomposition) of the crystals was visible after several weeks on the shelf.

As a test of the *o*-aminobenzoylating potential of **5**, the reaction of the active ester with benzylamine as the model nucleophile was investigated. When freshly prepared solutions of **5** in dioxan were treated, *in situ*, with benzylamine, *N*-benzylanthranilamide (**7a**) was isolated from the resulting mixture in yields up to 55%. The yield of **7a** was increased to almost 90% by reacting the pure active ester with benzylamine at 100 °C. The latter method is comparable to the previously reported[10] reaction of the triazine active ester **4** with benzylamine. Both active esters **4** and **5** are superior to isatoic anhydride (**1**) as *o*-aminobenzoylating agents; in our hands, reaction of **1** with benzylamine gave, on average, a 60% yield of the amide **7a**.

Comparison of the reactions of **1** and **5** with the sterically hindered nucleophile, *t*-butylamine, is even more striking. Isatoic anhydride reacted with *t*-butylamine vigorously, but gave only a 13% yield of the *N*-*t*-butylanthranilamide (**7b**); Staiger and Miller[8] stated that reaction of *t*-butylamine with **1** gives predominantly the ureido acid, but did not report the actual yield of **7b** obtained by their method. Reaction of *t*-butylamine with the active ester **5** by the *in situ* method gave a significantly higher yield (30%) of the amide **7b**, and a much higher yield (71%) of **7b** was obtained by refluxing of the pure active ester in *t*-butylamine. These results are summarised in the Table.

Further illustration of the potential of **5** was observed in reaction with diethylamine. In the reported reactions[8] of isatoic anhydride with secondary amines, only the ureido acids were isolated; anthranilamide yields were so small as to be unisolable. By contrast, the active ester **5** reacts readily with diethylamine to give a fair yield (42%) of the diethylamide **7c**.

Condensation of anthranilic acid with *N*-hydroxyphthalimide by the diimide method afforded *N*-(*o*-aminobenzoyloxy)-phthalimide (**6**), but in lower yield than that of the succinimide analogue. Although the phthalimide active ester **6** reacted with benzylamine, the yield of amide **7a** was poor and it appears that **6** is not as effective as **5** in *o*-aminobenzoylation. The application of **5** and **6** in synthesis does not extend to the preparation of anthranilate esters. Neither active ester showed any tendency to react with potassium *t*-butoxide in *t*-butanol.

Table. Anthranilamides Prepared from Active Ester of Anthranilic Acid and Amines

Substrate	Nucleophilic amine	Product	Yield [%][a]	Method
1	$C_6H_5CH_2NH_2$	**7a**	60	Lit.[8]
4	$C_6H_5CH_2NH_2$	**7a**	90	Lit.[10]
5	$C_6H_5CH_2NH_2$	**7a**	55	A
5	$C_6H_5CH_2NH_2$	**7a**	89	B
6	$C_6H_5CH_2NH_2$	**7a**	<17	C
1	t-$C_4H_9NH_2$	**7b**	13	Lit.[8]
5	t-$C_4H_9NH_2$	**7b**	30	A
5	t-$C_4H_9NH_2$	**7b**	71	B
5	$(C_2H_5)_2NH$	**7c**	42	B

[a] All yields presented are those obtained by us.

***N*-(*o*-Aminobenzoyloxy)-succinimide (5):**
Anthranilic acid (6.85 g, 0.05 mol), *N*-hydroxysuccinimide (11.5 g, 0.10 mol), dicyclohexylcarbodiimide (10.3 g, 0.05 mol), and 4-dimethylaminopyridine (1.0 g, 0.008 mol) are mixed and dissolved in the minimum volume of anhydrous redistilled dioxan (~600 ml) at room temperature. The mixture is stirred for 48 h and the precipitate of dicyclohexylurea is removed by filtration. The filtrate, containing the active ester **5**, is either used *in situ* as described in Method A below, or is treated as follows to isolate the pure active ester. The solution is evaporated to dryness under vacuum. The oily residue is taken up in chloroform (250 ml), filtered to remove insoluble impurity, and the clear solution washed with aqueous normal sodium hydroxide solution (3 × 100 ml), then with water (3 × 100 ml), and dried with magnesium sulfate. Evaporation of the dried chloroform solution gives an oily residue, which solidifies slowly and is recrystallised from 1-propanol to afford the pure active ester **5**; max. yield: 52%; m.p. 161.5–163 °C (pale green plates).

$C_{11}H_{10}N_2O_4$	calc.	C 56.41	H 4.30	N 11.96
(234.2)	found	56.29	4.18	11.82

I.R. (nujol): ν = 3510, 3400, 1730 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.87 (s, 4H, methylene); 5.70 (broad s, 2H, NH_2); 6.5–8.1 ppm (m, 4H_{arom}).

***N*-(*o*-Aminobenzoyloxy)-phthalimide (6):**
Anthranilic acid and *N*-hydroxyphthalimide[15] are condensed using the diimide method described above. The ester **6** is recrystallised from 1-propanol/dimethyl sulfoxide as yellow prisms; yield: 22%; m.p. 190–195 °C.

$C_{15}H_{10}N_2O_4$	calc.	C 63.83	H 3.57	N 9.92
(282.2)	found	63.53	3.51	9.78

I.R. (nujol): ν = 3480, 3370, 1730 cm^{-1}.

***N*-Benzylanthranilamide (7a):**
Method A: *(in situ)*: Anthranilic acid and *N*-hydroxysuccinimide are condensed by the diimide method described above. The solution of the active ester in dioxan is treated with an equimolar amount of benzylamine at room temperature and the reaction was followed by T.L.C. (the active ester **5** has R_F = 0.56 on Merck F-254 silica gel with 10% methanol in chloroform) until the conversion of the active ester is complete (~48 h). The dioxan is removed under vacuum and the oily residue is taken up in chloroform, washed thoroughly with aqueous sodium hydroxide and then with water. Evaporation of the dried (magnesium sulfate) chloroform solution and recrystallisation of the residue from benzene/petroleum ether gives the *N*-benzylanthranilamide **7a**; yield: 55%; m.p. 122–123 °C (Lit.[14], m.p. 123 °C).

I.R. (nujol): ν = 3480, 3360, 3300 (br), 1630 cm^{-1}.

This product is identical (I.R. and mixture m.p.) with a sample prepared from isatoic anhydride and benzylamine by the method of Staiger and Miller[8].

Method B: *N*-(*o*-Aminobenzoyloxy)-succinimide (0.35 g, 0.0015 mol) is mixed with benzylamine (1.4 ml) and the mixture heated at 100 °C for 0.5 h. The residue is taken up in chloroform (25 ml),

washed thoroughly with water (3 × 10 ml), dried with magnesium sulfate, and evaporated. Recrystallisation of the residue from benzene/petroleum ether affords **7a**; yield: 0.30 g (89%).

Method C: *N*-(*o*-Aminobenzoyloxy)-phthalimide (**6**; 140 mg, 0.0005 mol) is heated with benzylamine (180 mg, 0.0017 mol) at 100 °C for 0.5 h and worked up as described in Method B. The benzene/petroleum ether-soluble fraction (yield: 20 mg) contains the amide **7a** ($R_F = 0.65$, thin layer chromatography on silica gel F-254 Merck with 10% methanol in chloroform).

***N*-(*t*-Butyl)-anthranilamide (7b):**

(1): *N*-(*o*-Aminobenzoyloxy)-succinimide (0.35 g, 0.0015 mol) is dissolved in excess *t*-butylamine (2.0 ml) and refluxed for 1.0 h. The butylamine is removed under vacuum and the residue washed with water (2 × 5 ml). The insoluble solid is the *N*-(*t*-butyl)-anthranilamide **7b**; yield: 0.20 g (71%); m.p. 123–125 °C (from benzene).

I.R. (nujol): $\nu = 3480, 3370, 3320, 1630\ cm^{-1}$.

(2): Reaction of the active ester with *t*-butylamine by Method A, described above, affords the same anthranilamide **7b**; yield: 30%.

(3): Reaction of *t*-butylamine with isatoic anhydride by the method of Staiger and Miller[8] gives the amide **7b**; yield: 13%; identical (I.R. and mixture m.p.) with a sample prepared from the active ester.

***N,N*-Diethylanthranilamide (7c):**

N-(*o*-Aminobenzoyloxy)-succinimide (0.35 g, 0.0015 mol) is treated with diethylamine (1.0 ml) and heated at the boiling point (56 °C) for 0.5 h. The mixture is triturated with petroleum ether (30–60 °C) and the petroleum ether layer decanted. Evaporation of the petroleum ether affords the *N,N*-diethylamide as a pale yellow oil; yield: 0.12 g (42%).

I.R. (nujol): $\nu = 3350, 3240, 1620\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.15$ (t, $J = 7$ Hz, 6H, methyl); 3.40 (q, $J = 7$ Hz, 4H, methylene); 4.1 (broad s, 2H, NH_2); 6.5–7.3 ppm (m, $4H_{arom}$).

This research was supported by a grant from the Natural Sciences and Engineering Research Council of Canada. Microanalyses were carried out by the Canadian Microanalytical Service, Vancouver, B.C.

Received: January 7, 1980
(Revised form: February 28, 1980)

[1] M. Manhas, S. Amin, *J. Heterocycl. Chem.* **14**, 161 (1977).
[2] A. Santilli, J. Osdene, *J. Org. Chem.* **29**, 2717 (1964).
[3] M. Gibson, M. Green, *Tetrahedron* **21**, 2191 (1965).
[4] N. Heindel, T. Lemke, *J. Heterocycl. Chem.* **3**, 389 (1966).
[5] G. M. Coppola, R. I. Mansukhani, *J. Heterocycl. Chem.* **15**, 1169 (1978).
[6] F. D. Eddy, M. F. G. Stevens, K. Vaughan, *Can. J. Chem.* **56**, 1616 (1978).
[7] R. P. Staiger, E. C. Wagner, *J. Org. Chem.* **18**, 1427 (1953).
[8] R. P. Staiger, E. B. Miller, *J. Org. Chem.* **24**, 1214 (1959).
[9] R. L. Jacobs, *J. Heterocycl. Chem.* **7**, 1337 (1970).
[10] T. P. Ahern, T. Navratil, K. Vaughan, *Can. J. Chem.* **55**, 630 (1977).
[11] Y. Elkana, *Bayer-Symposium V: Proteinase Inhibitors*, Springer Verlag, 1974, p. 445.
[12] G. W. Anderson, J. E. Zimmerman, F. M. Callahan, *J. Am. Chem. Soc.* **86**, 1839 (1964).
[13] G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **90**, 602 (1978); *Angew. Chem. Int. Ed. Engl.* **17**, 569 (1978).
[14] R. Anet, S. Somasekhara, *Can. J. Chem.* **38**, 746 (1960).
[15] Prepared by L. L. Mossman and S. L. Foster as part of an undergraduate synthesis project.

0039-7881/80/0932-0721 $ 03.00