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N-[O-1,2,3-Benzotriazin-4(3H)one-yl]-3,(2-pyridyldithio)propionate: A More Reactive Alternative To SPDP[1]

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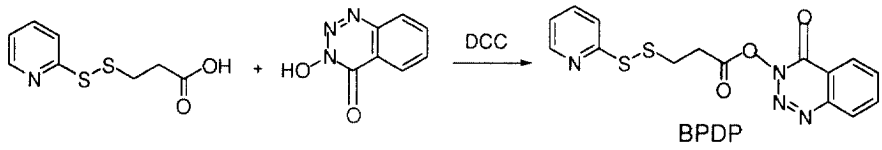
Abstract: *N*-[O-1,2,3-Benzotriazin-4(3H)one-yl]-3-(2-pyridyldithio)propionate [BPDP] has been synthesized and found to react with secondary amines to give high yields of acylated product. In sharp contrast, the widely used heterobifunctional coupling reagent, N-[O-succinimdyl]-3-(2-pyridyldithio) propionate [SPDP] afforded low to negligible yields of product.

During the course of our studies involving the synthesis umbrella-like amphiphiles, we sought a method for attaching an activated thiol group to a secondary amine.[2] Although N-[O-succinimdyl]-3-(2-pyridyldithio)propionate [SPDP] has been widely used for analogous transformations of primary amines, the applicability of this reagent to secondary amines has not previously been reported.[3] In this paper we show that the synthetic utility of SPDP is, in fact, limited to primary amines, but that simple replacement of the N-[O-succinimdyl] group with *N*-[O-1,2,3-benzotriazin-4(3H)one-yl] leads to a heterobifunctional coupling reagent that effectively acylates secondary amines.

N-[O-1,2,3-Benzotriazin-4(3H)one-yl]-3-(2-pyridyldithio)propionate [BPDP] was synthesized by direct coupling of 3-(2-pyridyldithio)propionic acid with *N*-O-1,2,3-benzotriazin-4(3H)one, using DCC as a condensing agent.[3,4] "Head to head" comparisons were then made between SPDP and BPDP for the acylation of a series of secondary amines. Isolated yields and reaction times that are reported in Table 1 reveal substantially greater reactivity of BPDP relative to SPDP.



The ability of BPDP to effectively acylate secondary amines should encourage the development of new classes of modifying agents.[5] In particular, it should provide a convenient route to new families of compounds derived from *secondary* amines that can be used for modifying metal surfaces (e.g., gold electrodes), and thiol-bearing membrane surfaces (e.g., liposomes), and biopolymers (e.g., proteins). It is on this basis that BPDP is expected to become a valuable addition to the current arsenal of heterobifunctional coupling agents.

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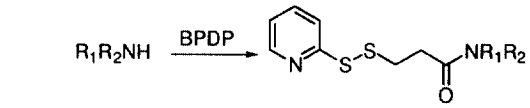
GENERAL PROCEDURE: All reactions that are reported in the Table 1 were carried out on a mmol scale, using amine concentrations ranging from 0.05 to 0.2 M. To a solution of secondary amine (1 equiv) and N,N-diisopropyl-N-ethylamine (2 equiv) in an appropriate solvent was added a solution of 1.1 equiv of BPDP or SPDP in CH_2Cl_2. The reaction mixture was stirred at rt for the indicated period of time. All acylated products (isolated by column chromatography, silica gel), gave the expected HRMS.

Table 1. Synthetic Utility of BPDP



Organic Amine	*Reagent*	*Time (h)*	*Solvent*	*Isolated Yield(%)*
R_1=R_2= CH_3	BPDP (SPDP)	4 (48)	a	82 (50)[6a]
R_1=R_2= $CH_2CH_2CH_3$	BPDP (SPDP)	5 (24)	b	70 (10)[6b]
R_1=R_2= $(CH_2)_{17}CH_3$	BPDP (SPDP)	4 (24)	b	82 (8)[6c]
R_1=R_2= CH_2CH_2OH	BPDP (SPDP)	8 (24)	c	79 (3)[6d]
R_1=R_2= CH_2CO_2Na	BPDP (SPDP)	4 (24)	a	87 (0)[6e]
Proline	BPDP (SPDP)	2 (24)	a	69 (5)[6f]

[a = $CH_2Cl_2/CH_3OH/H_2O$, 1/2/1 (v/v/v); b = CH_2Cl_2; c = CH_2Cl_2/CH_3OH, 1/1 (v/v)]

References and Notes

1) We thank the National Institutes of Health (PHS Grant GM51814) for support of this research.
2) Janout, V.; Lanier, M.; Regen, S. L., *J. Am. Chem. Soc.*, **1997**, *119*, 640.
3) Carlsson, J.; Drevin, H.; Axen, R., *Biochem. J.*, **1978**, *173*, 723.
4) BPDP: mp 59-61°C; ^{1}H NMR ($CDCl_3$): 3.15-3.17 (m, 4H), 7.10 (t, 1H), 7.65 (m, 2H), 7.82 (t, 1H), 7.98 (t, 1H), 8.19 (d, 1H), 8.33 (d, 1H), 8.49 (d, 1H); ^{13}C NMR ($CDCl_3$): 167.74, 159.04, 149.80, 144.23, 137.21, 135.42, 132.75, 128.97, 125.69, 122.15, 120.97, 120.01, 32.75, 31.21. Anal. Calcd ($C_{15}H_{12}N_4O_3S_2$): C, 49.99; H, 3.36; N, 15.55. Found: C, 49.83; H, 3.45; N, 15.54.
5) In preliminary studies, BPDP has been used to conjugate glutathione to a molecular umbrella; i.e., N^1,N^3-spermidinebis[cholic acid amide]: Janout, V.; Regen, S. L., unpublished results.
6) (a) ^{1}H NMR: 2.72 (t, 2H), 2.89 (s, 6H), 3.03 (t, 2H), 7.04 (m, 1H), 7.61 (t, 1H), 7.70 (d, 1H), 7.40 (d, 1H); ^{13}C NMR ($CDCl_3$): 170.49, 160.14, 149.61, 149.41, 137.07, 136.86, 36.86, 35.30, 33.77, 32.54. (b) ^{1}H NMR (CDCl3): 0.84 (t, 6H), 1.50 (m, 4H), 2.72 (t, 2H), 3.06 (m, 4H), 3.23 (t, 2H), 7.05 (m, 1H), 7.62 (t, 1H), 7.72 (d, 1H), 8.43 (d, 1H); ^{13}C NMR ($CDCl_3$): 170.04, 160.95, 149.45, 137.14, 120.57, 119.57, 49.42, 47.63, 34.12, 32.48, 22.07, 20.85, 11.26. (c) ^{1}H NMR (CDCl3): 0.87 (t, 6H), 1.26 (s, 60H), 1.48 (m, 4H), 2.72 (t, 2H), 3.09 (m, 4H), 3.27 (t, 2H), 7.04 (m, 1H), 7.58 (t, 1H), 7.71 (d, 1H), 8.43 (d, 1H); ^{13}C NMR ($CDCl_3$): 169.92, 160.26, 149.40, 136.87, 120.45, 47.84, 46.07 34.11, 31.86, 29.30-29.62 (m), 27.71, 27.00, 26.84, 22.63, 14.10. (d) ^{1}H NMR ($CDCl_3$): 2.84 (t, 2H), 3.05 (t, 2 H), 3.42 (t, 2H), 3.50 (t, 2H), 3.71 (t, 2H), 3.77 (t, 2H), 3.99 (bs, 2H), 7.07 (m, 1H), 7.62 (t, 1H), 7.72, (d, 1H) 8.39, (1H). ^{13}C NMR ($CDCl_3$): 172.67, 160.01, 149.35, 137.20, 120.80, 120.24, 61.09, 60.56, 52.09, 50.64, 33.62, 33.07. (e) ^{1}H NMR (CD_3OH): 2.81 (t, 2H), 3.08 t, 2H), 3.96 (s, 4H), 6.87 (m, 1H), 7.44 (m, 2H), 8.40 (md, 1H); ^{13}C NMR (CD_3OH): 175.90, 173.88, 161.42, 150.36, 139.28, 122..29, 121.12, 54.34, 52.08, 35.68, 33.77. (f) ^{1}H NMR ($CDCl_3$): 1.76-2.06 (m, 4H), 2.54 (m, 2H), 2.89 (m, 2H), 3.21-3.37 (m, 2H), 4.23 (m, 1H), 7.01 (m, 1H) 7.57 (t, 1H), 7.64 (d, 1H), 8.25 (d, 1H). ^{13}C NMR ($CDCl_3$): 178.10, 170.21, 160.18, 149.65, 137.24, 120.78, 119.82, 61.86, 47.31, 33.85, 33.64, 29.65, 24.71.