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NEW SYNTHETIC "TRICKS".
ONE-POT PREPARATION OF N-SUBSTITUTED PHTHALIMIDES FROM AZIDES AND PHTHALIC ANHYDRIDE

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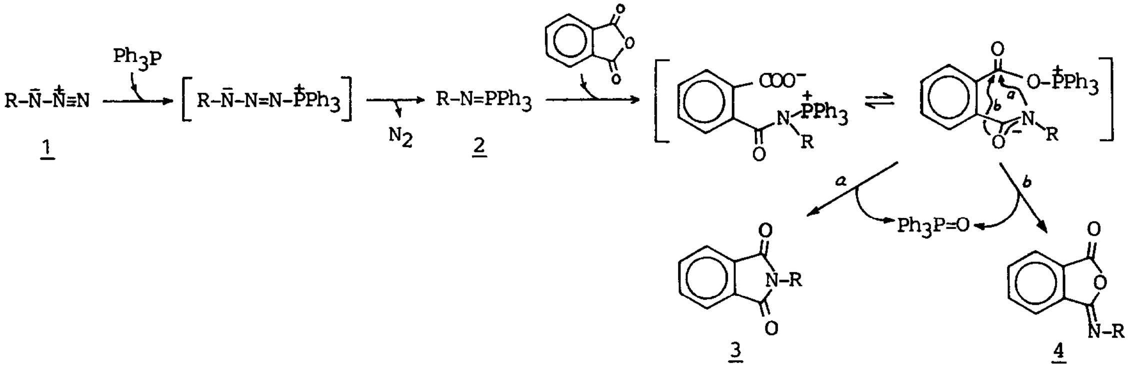
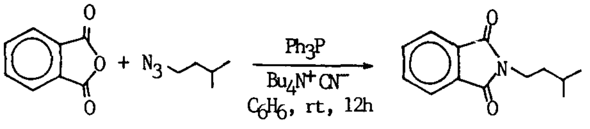
N-Substituted phthalimides can be obtained in very good yields, under essentially neutral conditions, by mixing or heating an alkyl (or aryl) azide, triphenylphosphine, and phthalic anhydride in benzene or toluene, in the presence of a catalytic amount of tetrabutylammonium cyanide. Application of the reaction into the domain of carbohydrates is promising.

The phthaloyl group is a common protecting group for amines: the amine is allowed to react with phthalic anhydride (or with a related compound) and the resulting intermediate is then heated to cause the intramolecular condensation to the desired phthalimide;[1] *the phthalolyl group not only blocks the amine but may change the reactivity of either the vicinal carbon atoms or substituents (by steric hindrance, by anchimeric assistance...); finally, its cleavage is normally accomplished by means of hydrazine. When milder conditions than those just indicated are required, the phthalimido group can be entered via the Mitsunobu reaction,*[2] *from the alcohol and phthalimide.*[3] *However, unsatisfactory yields are sometimes obtained, since dehydration—a reaction also promoted by the EtOCO-N=N-COOEt/*Ph_3P *reagent—instead of substitution takes often place.*

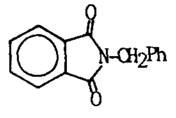
We propose here a new, alternative way for the preparation of phthalimido derivatives, which starts from azides (1) and converts them into the corresponding phosphazenes or phosphine imides (2),[4] *these compounds reacting* in situ *with phthalic anhydride. In preliminary experiments we observed that compounds 2 reacted quickly with phthalic anhydride to give intermediates that were more slowly converted into mixtures of the phthalimido derivatives (3) and their isomers 4 in similar amounts. Isoimides 4 appeared to be easily hydrolyzed to the monoamide of phthalic acid during the workup. The overall yields were consequently low. We report here that the presence of 0.1 equiv. of tetrabutylammonium cyanide isomerizes quantitatively 4 into the desired, thermodynamically favoured*[5] *3 (no matter whether* Bu_4N^+ CN^- *is added at the beginning or at the end of the reaction).*



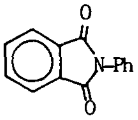
Our results can be summarized as follows:



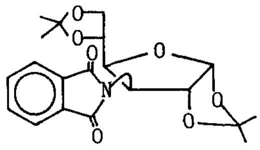
5 (99%)



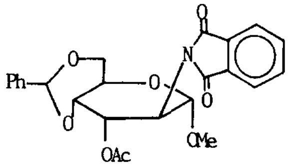
6, CH_2Cl_2, rt, 12h, 96%



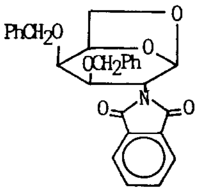
7, C_6H_6, Δ, 18h, 86%



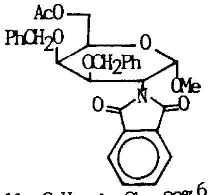
8, C_7H_8, Δ, 48h, 88%



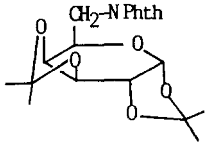
9, C_7H_8, Δ, 24h, 86%



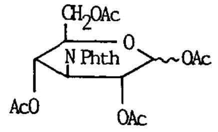
10, C_6H_6, Δ, 10h, 98%



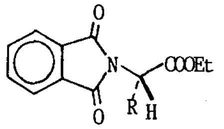
11, C_6H_6, Δ, 8h, 89%[6]



12, C_6H_6, Δ, 48h, 83%



13, C_6H_6, Δ, 42h, 81%[7]



14, R=H, C_6H_6, rt, 12h, 81%
15, R=Me, C_6H_6, Δ, 6h, 85%
16, $R=CH_2CHMe_2$, C_6H_6, Δ, 36h, 71%[8]

Usually, 1.0 mmols of the azide, 288 mg (1.1 mmols) of Ph_3P, 163 mg (1.1 mmols) of phthalic anhydride just purified by sublimation, and ca. 27 mg of anh. $Bu_4N^+CN^-$ were dissolved in 5-10 ml of anh. benzene or toluene, under N_2. In the case of 5, 6, and 14 stirring overnight at room temperature was sufficient to obtain a practically quantitative conversion (TLC). On the other hand, for the more hindered azides heating in toluene at reflux was necessary to enhance the reactivity of the phosphazene with phthalic anhydride. Afterwards, the organic solutions were concentrated, and phthalimides[9] were easily separated by column chromatography (either with CH_2Cl_2 or C_6H_{14}/AcOEt) on silica gel.

Some advantages are inherent to this new "trick" for protecting amino groups: i) extremely good yields are obtained under one-pot, quite smooth conditions; ii) chiral centres remain unaltered, as expected, since they are not involved in the reaction and since, even though in some cases epimerization or racemization might occur, the conditions are essentially neutral; iii) application to natural products seems promising especially in carbohydrate chemistry:[10] compounds with phthalimido groups at C-2 like 10 and 11 are very effective for the synthesis, from derivatives of 2-amino sugars, of disaccharides (or oligosaccharides) with β-glycosydic linkages.[11]

References and footnotes

1.- A.K.Bose, in *Org.Synth.* Coll. Vol. V, Wiley, New York, 1973. E.Hoffmann and H.Schiff-Shenhav, *J.Org.Chem.*,*27*, 4686(1962). D.A.Hoogwater, D.N.Reinhoudt, T.S.Lie, J.J.Gunneweg, and H.C.Beyerman, *Rec.Trav.Chim.Pays-Bas*,*92*,819 (1973). For a review, see T.W.Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1981.
2.- Review: O.Mitsunobu, *Synthesis*,1(1981).
3.- See, e.g., M.Chmielewski, J.Jurczak, and A.Zamojski, *Tetrahedron*,*34*,2977(1978) and ref. therein.
4.- For a recent review on the Staudinger reaction (i.e. 1→2) see Yu.G.Gololobov, I.N.Zhmurova, and L.F.Kasukhin, *Tetrahedron*,*37*,437(1981).
5.- It is known that most isoimides rearrange to the corresponding imides at high temperature. See G.V.Boyd and R.L. Monteil, *J.Chem.Soc.*,*PT-1*,1338(1978), W.R.Rodericj and P.L.Bhatia, *J.Org.Chem.*,*28*,2018(1963), and ref. therein.
6.- When the reaction was performed without $Bu_4N^+CN^-$, in refl. benzene for 10h, separation by column chromatography afforded 11 in 37% yield and the corresponding isoimide in 35% yield.
7.- The reaction was actually carried out with a mixture of anomers (88% of anomer α, 12% of anomer β).
8.- In this case, the phosphine imide was generated from ethyl leucinate hydrochloride, Ph_3PBr_2 (1.05 equiv.), and NEt_3 (3.3 equiv.).
9.- The structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, and IR spectroscopy, and also, in some cases, by comparison with known, authentic samples. Satisfactory microanalyses were obtained for the new products.
10.-Several phosphazenes arising from azido sugars have been formerly reported to afford either carbodiimides or cyclic carbamates (with CO_2) and aziridine derivatives (e.g., from some 3-N_3-2-OTs derivatives). See A.Messmer, I.Pintér, and F.Szegö, *Angew.Chem.Int.Ed.*,*3*,228(1962), J.Kovács, I.Pintér, A.Messmer, and G.Tóth, *Carbohydr.Res.*,*141*,57(1985), & ref.th.
11.-Review: H.Paulsen, *Angew.Chem.Int.Ed.*,*21*,155(1982).

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