Dichloromethylenation of Substitutued 1*H*-Isoindole-1,3-(2*H*)-diones (Phthalimides)

Denise Robinson, Alan L. Stanley, and Stephen P. Stanforth*

Department of Chemical and Life Sciences, University of Northumbria at Newcastle, Newcastle upon Tyne, NE1 8ST, UK

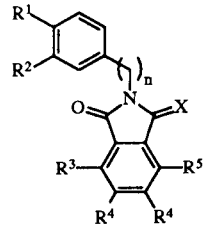
Received January 17, 1995

A number of substituted 1*H*-isoindole-1,3-(2*H*)-dione derivatives (phthalimides) underwent dichloromethylenation when reacted with a mixture of triphenylphosphine and carbon tetrachloride.

J. Heterocyclic Chem., **32**, 783 (1995).

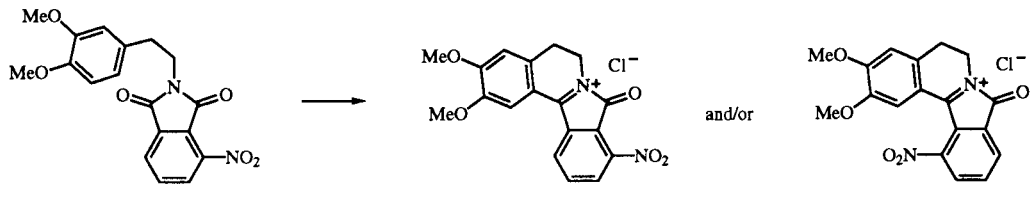
In relation to our earlier studies in isoquinoline chemistry [1], we were interested in preparing phthalimide derivative **13** and effecting the ring closure reaction shown in the Scheme. A mixture of triphenylphosphine and carbon tetrachloride is known to convert amides to imidoyl chlorides [2] and this mixture has been used recently [3] to convert amides derived from 2-phenylethylamine into substituted 3,4-dihydroisoquinolines *via* imidoyl chlorides in a Bischler Napieralski reaction. When phthalimide derivative **13** was treated with this mixture however, intramolecular cyclisation as depicted in the Scheme had not occurred but the dichloromethylene derivative **14** was isolated in 15% yield. Triphenylphosphine and carbon tetrachloride is well known for the dichloromethylenation of ketones [2] in a Wittig type reaction in which dichloromethylenetriphenylphosphorane is the active reagent and a similar process is presumably responsible for the transformation of phthalimide derivative **13** into the product **14**. We have tentatively assigned structure **14** to the reaction product rather than the alternative regioisomeric structure **15** because structure **14** is derived from the Wittig reaction at the least crowded carbonyl group. Further evidence to support this assignment is given below.

A series of substituted phthalimides was next prepared and their dichloromethylenation reactions were investigated. Compounds **1** and **3** gave the corresponding products **2** (31% yield) and **4** (40% yield). The reaction of the dichloro derivative **5** failed to go to completion and, after purification of the crude reaction mixture by column chromatography, a 3:2 mixture of starting material **5** and product **6** was obtained. Fractional recrystallisation from ethanol failed to give pure product **6**. The tetrachloro derivative **7** was unreactive under the reaction conditions and no compound **8** could be detected. The failure of compound **7** to react was attributed to steric effects, the approach and reaction of the bulky dichloromethylenetriphenylphosphorane is hindered by the chlorine atoms adjacent to the carbonyl groups and for this reason the dichloromethylenation reaction product of compound **13**



	n	R^1	R^2	R^3	R^4	R^5	X
1	1	H	H	H	H	H	O
2	1	H	H	H	H	H	CCl_2
3	2	H	H	H	H	H	O
4	2	H	H	H	H	H	CCl_2
5	2	H	H	H	Cl	H	O
6	2	H	H	H	Cl	H	CCl_2
7	2	H	H	Cl	Cl	Cl	O
8	2	H	H	Cl	Cl	Cl	CCl_2
9	2	OMe	H	H	H	H	O
10	2	OMe	H	H	H	H	CCl_2
11	2	OMe	OMe	H	H	H	O
12	2	OMe	OMe	H	H	H	CCl_2
13	2	OMe	OMe	NO_2	H	H	O
14	2	OMe	OMe	NO_2	H	H	CCl_2
15	2	OMe	OMe	H	H	NO_2	CCl_2

Scheme



13

has been assigned the structure **14**. The methoxy derivatives **9** and **11** both gave the dichloromethylene derivatives **10** and **12** respectively (39% and 47% yield) as expected.

A comparison of the proton nmr spectra of the reactants and products was informative and allowed us to be certain that dichloromethylenation of compound **5** had occurred even though we could not isolate the product **6** in the pure state. Phthalimide derivatives which possessed a 2-phenylethyl or substituted 2-phenylethyl group all exhibited a triplet at approximately 3.90 ppm which was attributed to the methylene protons located at the 1-position of this group. After dichloromethylenation, this triplet moved downfield by approximately 0.5 ppm. The benzylic protons in compound **1** underwent a similar but slightly larger (0.7 ppm) downfield shift after dichloromethylenation.

EXPERIMENTAL

Proton nmr spectra were determined at 90 MHz in deuteriochloroform solution. Infra-red spectra were recorded as potassium bromide discs. 1-*H*-Isoindole-1,3-(2*H*)-diones derivatives **1** [4], **3** [5] and **9** [6] have been reported previously.

1-*H*-Isoindole-1,3-(2*H*)-diones. General Method.

A mixture of the appropriate phthalic anhydride derivative, amine and triethylamine in toluene were heated at reflux (Dean-Stark) for 2 hours. The reaction mixture was allowed to cool to room temperature. Products either crystallised from the reaction mixture or were isolated by evaporation of the solvent followed by recrystallisation.

2-(2-Phenylethyl)-5,6-dichloro-1*H*-isoindole-1,3-(2*H*)-dione **5**.

4,5-Dichlorophthalic anhydride (1.79 g), 2-phenylethylamine (1.00 g) and triethylamine (0.83 g) in toluene (30 ml) gave compound **5**, 1.58 g (60%) as white needles, mp 161-163° (from acetonitrile); ir: ν 1700, 1400 and 1350 cm^{-1}; ^1H nmr: δ 7.89 (2H, s, ArH), 7.22 (5H, s, ArH), 3.90 (2H, t, J = 8 Hz, $-CH_2CH_2-$) and 2.97 (2H, t, J = 8 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{16}H_{11}NO_2Cl_2$: C, 60.0; H, 3.5; N, 4.4. Found: C, 58.95; H, 3.5; N, 4.4.

2-(2-Phenylethyl)-4,5,6,7-tetrachloro-1*H*-isoindole-1,3-(2*H*)-dione **7**.

3,4,5,6-Tetrachlorophthalic anhydride (2.36 g), 2-phenylethylamine (1.00 g) and triethylamine (0.83 g) in toluene (30 ml) gave compound **7**, 1.7 g (53%) as buff colored needles, mp 179-181° (from acetonitrile); ir: ν 1700, 1350 and 970 cm^{-1}; ^1H nmr: δ 7.25 (5H, m, ArH), 3.95 (2H, m, $-CH_2CH_2-$) and 3.00 (2H, m, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{16}H_9NO_2Cl_4$: C, 49.6; H, 2.3; N, 3.6. Found: C, 49.6; H, 2.15; N, 3.75.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1*H*-isoindole-1,3-(2*H*)-dione **11**.

Phthalic anhydride (4.08 g), 2-(3,4-dimethoxyphenyl)ethylamine (5.0 g) and triethylamine (5.60 g) in toluene (50 ml) gave compound **11**, 7.14 g (83%) as white leaflets, mp 176-178° (from ethanol); ir: ν 2940, 1710, 1515, 1395, 1275, 1230, 1145 and 1005 cm^{-1}; ^1H nmr: δ 7.75 (2H, m, ArH), 7.62 (2H, m, ArH), 6.72 (1H, s, ArH), 6.67 (2H, s, ArH), 3.85 (2H, t, J = 8 Hz, $-CH_2CH_2-$), 3.80 (3H, s, -OMe), 3.75 (3H, s, -OMe) and 2.88 (2H, t, J = 8 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.4; H, 5.5; N, 4.5. Found: C, 69.35; H, 5.35; N, 4.25.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-4-nitro-1*H*-isoindole-1,3-(2*H*)-dione **13**.

3-Nitrophthalic anhydride (5.45 g), 2-(3,4-dimethoxyphenyl)-ethylamine (5.12 g) and triethylamine (3.60 g) in toluene (100 ml) gave compound **13**, 8.0 g (83%) as pale yellow plates, mp 143-145° (from ethanol); ir: ν 1710, 1535, 1515, 1395, 1355, 1265, 1235, 1155, 1140, 1100 and 1025 cm^{-1}; ^1H nmr: δ 8.10 (3H, m, ArH), 6.80 (3H, m, ArH), 3.95 (2H, t, J = 8 Hz, $-CH_2CH_2-$), 3.89 (3H, s, -OMe), 3.82 (3H, s, -OMe) and 2.97 (2H, t, J = 8 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{18}H_{16}N_2O_6$: C, 60.7; H, 4.5; N, 7.9. Found: C, 60.75; H, 4.35; N, 7.95.

Dichloromethylenation Reactions. General Method.

A mixture of the appropriate substituted 1-*H*-isoindole-1,3-(2*H*)-dione derivative and triphenylphosphine in carbon tetrachloride were heated at reflux with stirring, allowed to cool to room temperature and then evaporated. The residue was purified by column chromatography over silica gel. Compound **7** was unreactive under these conditions.

2-Phenylmethyl-3-dichloromethylene-1*H*-isoindole-1-(2*H*)-one **2**.

Compound **1** (2.0 g), triphenylphosphine (5.5 g) and carbon tetrachloride (40 ml) for 6 hours gave, after column chromatography (eluent, petroleum ether:ethyl actate, 6:1), compound **2**, 0.79 g (31%) as a white powder, mp 111-112° (from ethanol); ir: ν 1700, 1350 and 975 cm^{-1}; ^1H nmr: δ 8.40 (1H, m, ArH), 7.95 (1H, m, ArH), 7.65 (2H, m, ArH), 7.25 (5H, m, ArH) and 5.45 (2H, s, $>CH_2$) ppm.

Anal. Calcd. for $C_{16}H_{11}Cl_2NO$: C, 63.2; H, 3.65; N, 4.6. Found: C, 62.95; H, 3.45; N, 4.7.

2-(2-Phenylethyl)-3-dichloromethylene-1*H*-isoindole-1-(2*H*)-one **4**.

Compound **3** (2.0 g), triphenylphosphine (6.33 g) and carbon tetrachloride (40 ml) for 6 hours gave, after column chromatography (eluent, petroleum ether:ethyl acetate 12:1 changing to 9:10), compound **4**, 1.0 g (40%) as a white powder, mp 108-109° (from ethanol); ir: ν 2800, 1700, 1400, 1000 and 700 cm^{-1}; ^1H nmr: δ 8.35 (1H, m, ArH), 7.88 (1H, m, ArH), 7.60 (2H, m, ArH), 7.22 (5H, s, ArH), 4.41 (2H, m, $-CH_2CH_2-$) and 3.00 (2H, m, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{17}H_{13}Cl_2NO$: C, 64.2; H, 4.1; N, 4.4. Found: C, 64.35; H, 3.9; N, 4.45.

2-(2-Phenylethyl)-3-dichloromethylene-5,6-dichloro-1*H*-isoindole-1-(2*H*)-one **6**.

Compound **5** (0.8 g), triphenylphosphine (1.64 g) and carbon tetrachloride (20 ml) for 5 hours gave, after column chromatography (eluent, hexane:ether, 3:1) a 3:2 mixture (0.43 g) of compound **5** and product **6**. The product ratio was determined by ^1H nmr spectroscopy (see text).

2-[2-(4-Methoxyphenyl)ethyl]-3-dichloromethylene-1*H*-isoindole-1-(2*H*)-one **10**.

Compound **9** (2.0 g), triphenylphosphine (6.7 g) and carbon tetrachloride (40 ml) for 6 hours gave, after column chromatography (eluent, petroleum ether:ethyl acetate, 6:1), compound **10**, 0.96 g (39%) as white needles, mp 80-81° (from ethanol); ir: ν 1700, 1500, 1250 and 1240 cm^{-1}; ^1H nmr: δ 8.35 (1H, m, ArH), 7.90 (1H, m, ArH), 7.58 (2H, m, ArH), 7.20 (2H, dd, J = 8 and 2 Hz, ArH), 6.80 (2H, dd, J = 8 and 2 Hz, ArH), 4.35 (2H, t, J = 8 Hz, $-CH_2CH_2-$), 3.80 (3H, s, -OMe) and 2.92 (2H, t, J = 8 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{18}H_{15}Cl_2NO_2$: C, 62.1; H, 4.3; N, 4.0. Found: C, 61.95; H, 4.25; N, 4.0.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-3-dichloromethylene-1*H*-isoindole-1-(2*H*)-one **12**.

Compound **11** (0.52 g), triphenylphosphine (1.05 g) (with a further addition of 0.2 g after 6 hours) and carbon tetrachloride (10 ml) for 12 hours gave, after chromatography (eluent, petroleum ether:ethyl acetate, 2:1), compound **12**, 0.30 g (47%) as a white powder, mp 129-130°; ir: ν 1700, 1610, 1350, 1260, 1235, 1114, 1105, 1030 and 920 cm^{-1}; ^1H nmr: δ 8.35 (1H, m, ArH), 8.00-7.40 (3H, m, ArH), 6.80-6.60 (3H, m, ArH), 4.32 (2H, t, J = 8 Hz, $-CH_2CH_2-$), 3.77 (3H, s, -OMe), 3.71 (3H, s, -OMe) and 2.85 (2H, t, J = 8 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{19}H_{17}Cl_2NO_3$: C, 60.3; H, 4.5; N, 3.7. Found: C, 60.55; H, 4.55; N, 3.7.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-3-dichloromethylene-7-nitro-1*H*-isoindole-1-(2*H*)-one **14**.

Compound **13** (0.54 g), triphenylphosphine (0.79 g) and carbon tetrachloride (15 ml) for 5 hours gave, after chromatography (eluent, petroleum ether:ethyl acetate, 3:1), compound **14**, 0.10 g (15%) as buff colored needles, mp 175-176° (from methanol); ir: ν 1715, 1535, 1510, 1350, 1260, 1145 and 1030 cm^{-1}; ^1H nmr: δ 8.65 (1H, t, J = 6 Hz, ArH), 7.78 (2H, m, ArH), 6.75 (3H, s, ArH), 4.41 (2H, t, J = 8 Hz, $-CH_2CH_2-$), 3.85 (6H, s, 2 x -OMe) and 2.95 (2H, t, J = 8 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_5 \cdot 0.5H_2O$: C, 52.7; H, 3.9; N, 6.6. Found: C, 52.45; H, 3.55; N, 6.7.

Aknowledgements.

We thank the SERC and Rhone Poulenc for a CASE award (to A. L. S.). We also thank Dr. M. P. L. Caton of Rhone Poulenc for useful advice and additional financial assistance.

REFERENCES AND NOTES

[1] A. L. Stanley and S. P. Stanforth, *J. Heterocyclic Chem.*, in press.

[2] R. Appel, *Angew. Chem., Int. Ed. Engl.*, **14**, 801 (1975).

[3] A. Bhattacharjya, P. Chattopadhyay, M. Bhaumik, and S. C. Pakrashi, *J. Chem. Res. (S)*, 228 (1989).

[4] H. F. Manske, *Org. Synth. Coll. Vol. II*, 83 (1943).

[5] I. Ganjian, M. Khorshidi, and I. Lalezari, *J. Heterocyclic Chem.*, **28**, 1173 (1991).

[6] M. Kulka and R. H. F. Manske, *J. Am. Chem. Soc.*, **75**, 1322 (1953).