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Synthesis of 3-Alkylidene Phthalimidines by Reaction of Isocyanates with Ortho-Manganated Aromatic Ketones.

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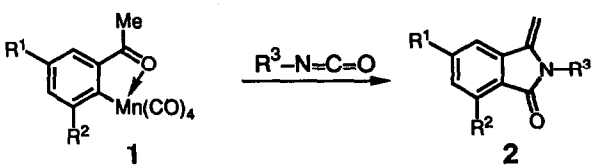
Abstract. Heating ortho-manganated aromatic ketones and R–N=C=O (R = Et, *n*-Pr, *p*-tolyl) in dioxane for 3 – 7 h leads to production of 3-alkylidene phthalimidines. The alkylidene phthalimidines derived from aliphatic isocyanates were unstable and were reduced to phthalimidines prior to purification and characterization.

Following up on recent disclosures that ortho-manganated acetophenones (1) react with alkynes and alkenes to produce ortho-functionalized products efficiently via insertion into the manganese carbon bond,[2–4] a survey of the reactions of ortho-manganated aromatic ketones with other unsaturated substrates was initiated. During the course of this study, it was discovered that isocyanates react with 1 producing, in most cases, good yields of 3-alkylidene phthalimidines (2), the core unit found in a number of isoindole derived alkaloid families (Eqn. 1).[5–7]

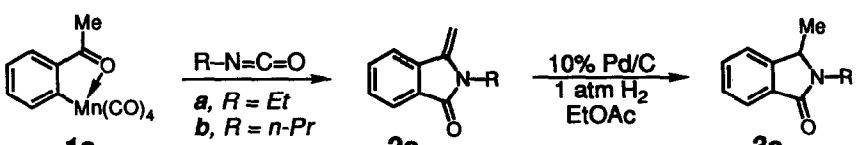
Eqn. 1



1 2

Heating a degassed dioxane solution of (η^2-2-acetylphenyl)tetracarbonylmanganese (**1a**), prepared from $PhCH_2Mn(CO)_5$ and acetophenone,[8,9] with three equivalents[10] of aliphatic isocyanate R–N=C=O (R = Et, *n*-Pr) in an oil-bath maintained at 90 °C for 3 h produced the unstable 3-methylidene phthalimidines **2a** and **2b** (Eqn. 2). Because alkylidene phthalimidines bearing an aliphatic substituent on nitrogen readily undergo autoxidation to phthalimides in air,[11,12] the reaction mixtures were freed of manganese impurities by chromatography and then hydrogenated to allow isolation of the stable phthalimidines, **3a** (64%) and **3b** (69%).[13,14]

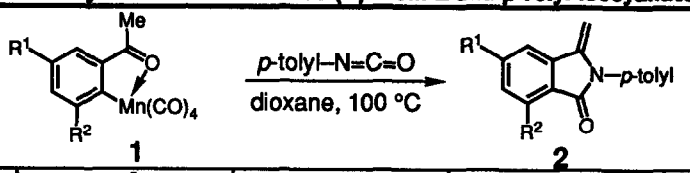
Eqn. 2



1a **2a** **2b** **3a** **3b**

Reaction of ortho-manganated acetophenones[15] with *p*-tolyl–N=C=O in dioxane at 100 °C for 13 h gave stable 3-methylidene phthalimidines (2c–2j) which were easily purified and characterized (Table).[16] The alkylidene phthalimidine synthesis is not restricted to ortho-manganated acetophenones. Manganese complex 4[4] reacted with *p*-tolyl isocyanate in dioxane to form compound 5 in 56% yield (Eqn. 3).

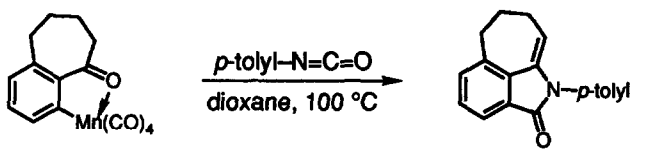
Table. Synthesis of Methylidene Phthalimidines (2) From 1 and *p*-Tolyl Isocyanate.



1 2

Entry	R^1	R^2	Compound	% yield
1	H	H	2c	76
2	H	F	2d	50
3	F	H	2e	52
4	H	Cl	2f	13
5	Cl	H	2g	63
6	H	MeO	2h	59
7	MeO	H	2i	69
8	CF_3	H	2j	37

Eqn. 3

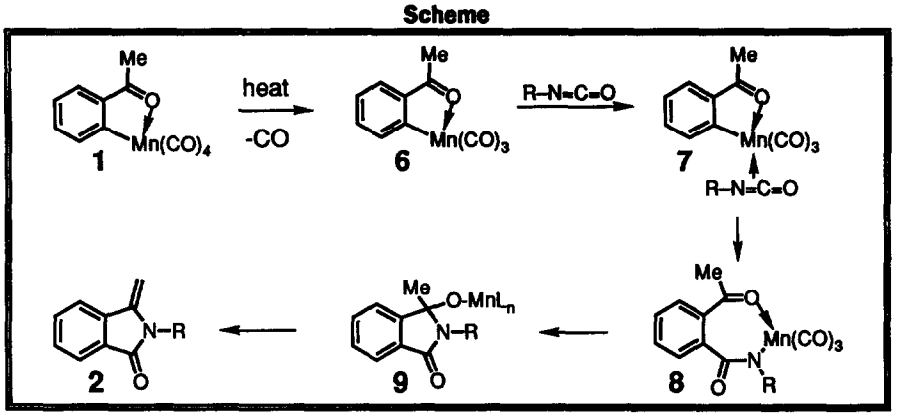


4 5

A reasonable mechanism for formation of the alkylidene phthalimidines is shown in the Scheme. Thermal generation of a coordinatively unsaturated species (6) via CO loss allows ligation of the isocyanate to the manganese giving 7 as a prelude to insertion of the N=C bond into the C–Mn bond which forms 8. Intramolecular condensation of the amide nitrogen with the carbonyl group would give intermediate 9 which should suffer facile elimination of "$HOMnL_n$" and produce the observed products.

The reaction of isocyanates with ortho-manganated aromatic ketones provides a novel method for the synthesis of alkylidene phthalimidines[7, 12, 17–19]. This is one of only a few reactions based on the insertion of isocyanates into transition metal–carbon bonds.[20]

Scheme



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References and Footnotes

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10. Excess R–N=C=O is required because of competing oligomerization of the isocyanate under the reaction conditions.

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13. General procedure for the preparation of 3-methyl-2-alkylphthalimidines, **3**: (η^2-2-Acetylphenyl)tetracarbonylmanganese (**1a**) (0.6 – 0.8 mmol) in 10 mL of dioxane was placed in a Schlenk tube equipped with a teflon-threaded vacuum valve. The alkyl isocyanate (3 equiv) was added and the solution was freeze-pump-thaw degassed and then placed under an argon atmosphere and the Schlenk tube was sealed. The reaction mixture was heated in an oil-bath maintained at 90 °C for a minimum of 3 h. After cooling to room temperature, the mixture was filtered through a plug of silica gel eluting with methylene chloride. The eluate was concentrated on a rotary evaporator and the crude product was initially purifed by rapid radial chromatography (Chromatotron, 2 mm SiO_2 rotor, 5 – 33% ethyl acetate/hexane). The product was immediately dissolved in 4 mL of EtOAc and transferred to a 25 mL Schlenk flask. Palladium (10%) on activated carbon (6.4 – 9.5 mg) was added, the reaction mixture was freeze-pump-thaw degassed and placed under one atm of H_2. After 12 h, the mixture was filtered through a short plug of Celite™ and the filtrate was concentrated on a rotary evaporator. The 3-methyl-2-alkylphthalimidines **3a,b** were purified by radial chromatography (Chromatotron, 2 mm SiO_2 rotor, 20 – 33% ethyl acetate/hexane). Typical IR absorption ≈1680 cm^{-1}.

14. All new compounds were characterized spectroscopically by IR, ^1H NMR, and ^{13}C NMR spectroscopy and gave satisfactory combustion analysis.

15. The preparation and characterization of the manganese complexes described in entries 2 – 8 of the Table are described in footnote 4.

16. General procedure for the preparation of 3-methylene-2-*p*-tolylphthalimidines, **2**: The manganese metallacycle **1** in the Table (0.4 – 0.5 mmol) in 5 – 10 mL dioxane was placed in a Schlenk tube equipped with a teflon-threaded vacuum valve. The *p*-tolyl isocyanate (3 equiv) was added and the solution was freeze-pump-thaw degassed. The reaction mixture was heated under argon in an oil-bath maintained at 100 °C for a minimum of 7 h. After cooling to room temperature, the mixture was filtered through a plug of SiO_2 with methylene chloride. After concentration of the eluate on a rotary evaporator and addition of 4 mL of methylene chloride, an insoluble white solid impurity was removed by filtration. The filtrate was concentrated and the residue was purified by radial chromatography (Chromatotron, 2 mm SiO_2 rotor, 5 – 33% ethyl acetate/hexane) providing the products, **2c – 2j**. Analytical samples were obtained by recrystallization from methylcyclohexane. Typical IR absorption ≈1710, 1640 cm^{-1}.

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