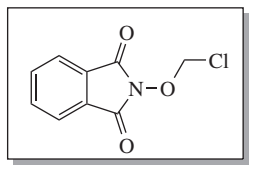
2-(Chloromethoxy)-1*H*-isoindole-1,3(2*H*)-dione

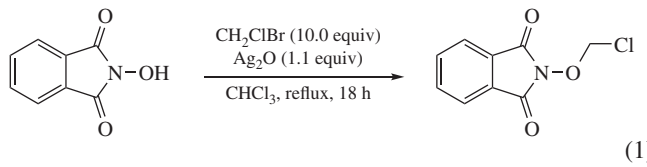


[22583-53-5] $C_9H_6ClNO_3$ (MW 211.61)

InChI = 1S/C9H6ClNO3/c10-5-14-11-8(12)6-3-1-2-4-7(6)9(11)13/h1-4H,5H2
InChiKey = ROYRVLUVVAXXCC-UHFFFAOYSA-N

(radical formylation reagent, electrophile)

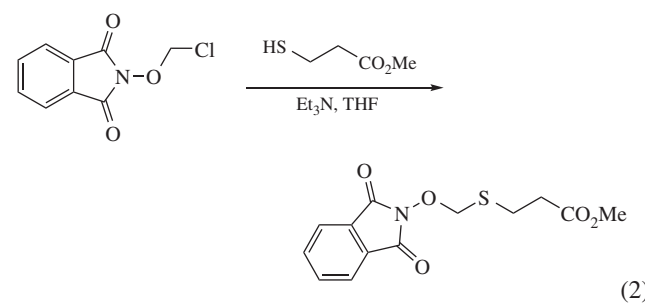
Alternative Name(s): N-chloromethoxyphthalimide.
Physical Data: white solid, mp 113–114 °C.
Solubility: chloroform, dichloromethane, acetonitrile, and most organic solvents.
Form Supplied in: commercially available as white solids.
Analysis of Reagent Purity: the reagent has been characterized by NMR spectroscopy. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, J = 5.5, 3.1 Hz, 2*H*), 7.81 (dd, J = 5.5, 3.1 Hz, 2*H*), 5.88 (s, 2*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 135.0, 128.8, 124.1, 83.8.
Preparative Methods: Commercially available or follow the steps below: *N*-hydroxyphthalimide (1.63 g, 10 mmol, 1.0 equiv) and CH_2ClBr (7.5 mL, 100 mmol, 10.0 equiv) in $CHCl_3$ (50 mL) were heated at reflux for 30 min, and then Ag_2O (2.54 g, 11 mmol, 1.1 equiv) was added with vigorous stirring. The suspension was stirred at 75 °C for 18 h under the dark, and the reaction mixture was then filtrated. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 20%) to afford *N*-chloromethoxyphthalimide (1.51 g, 71% yield) as a white solid[1] (eq 1).



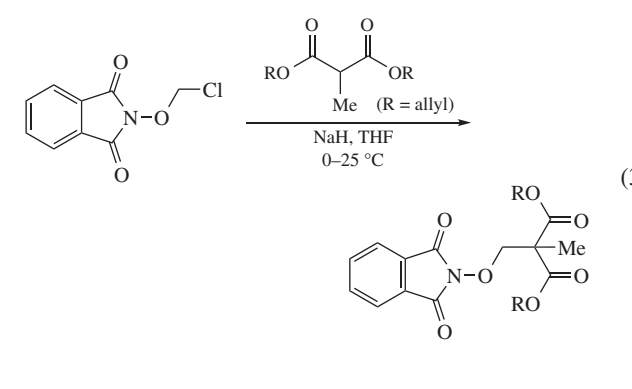
(1)

Purification: The reagent can be purified by silica gel chromatography (ethyl acetate/petroleum ether = 20%). Recrystallization from ethanol is an alternative method of purification.
Handling, Storage, and Precautions: The reagent can be stored in a cool and dry location. Stable as solids at ambient temperature for several months.

Reaction with Nucleophiles. Alkyl chlorides are stable carbon electrophiles. The title compound can be used as an electrophile in the reaction with appropriate thiols,[2] with Et_3N as the base and THF as the solvent (eq 2). Similarly, malonate ester is another reaction partner with 2-(chloromethoxy)-1*H*-isoindole-1,3(2*H*)-dione (eq 3). In this reaction, sodium hydride was used as the base to afford nucleophilic malonate anion, and then the title reagent was added to give the substituted product in 74% yield.[3]

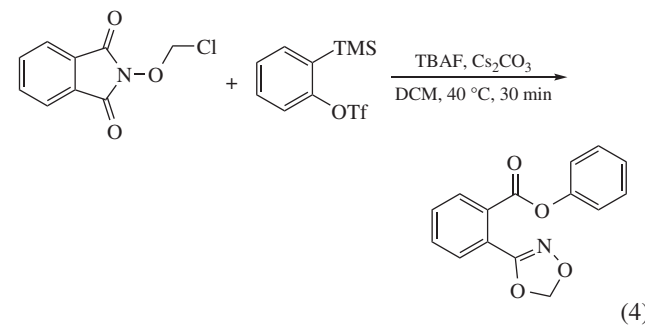


(2)



(3)

Reaction with Aryne. The title reagent reacts with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate to produce 1,4,2-dioxazole derivatives in 78% yield (eq 4).[4] In this reaction, the title reagent is hydrolyzed under basic conditions, followed by an intramolecular cyclization reaction to generate 2-(1,4,2-dioxazol-3-yl)benzoic acid. On the other hand, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate generates benzyne intermediate in the presence of TBAF. The nucleophilic attack of carboxylic acids to benzynes generates 1,4,2-dioxazoles (eq 5).



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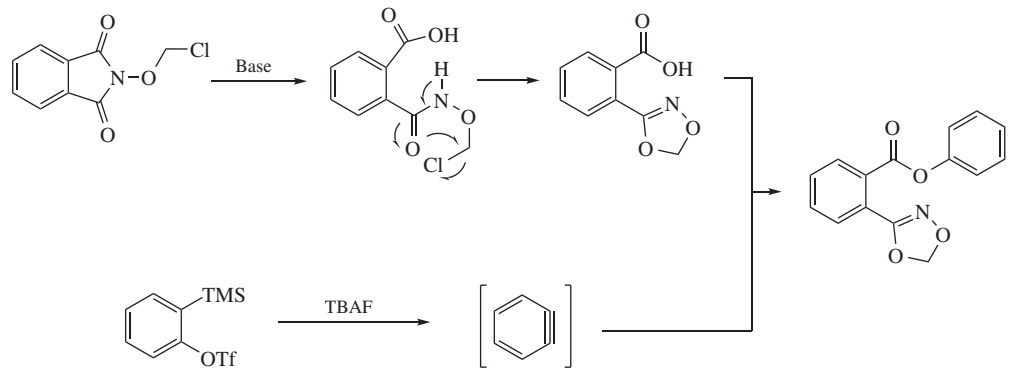
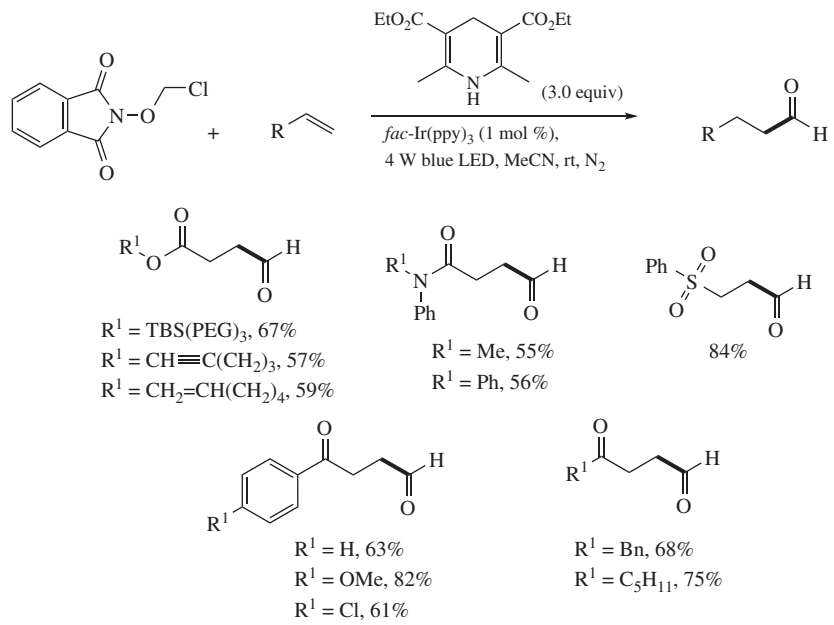


(5)

Radical Hydroformylation. Recently, 2-(chloromethoxy)-1*H*-isoindole-1,3(2*H*)-dione was reported as a new radical hydroformylation reagent that can react with various electron-deficient alkenes (eq 6).[5] In this reaction, with Hantzsch ester as reductant and *fac*-Ir(ppy)$_3$ as the photocatalyst, the formyl radicals were generated through the geminal HCl elimination of α-chloro alkoxy radicals. The sensitive functional groups such as silyl ethers, terminal alkynes, and terminal alkenes were tolerated to afford 4-oxobutanoates in 57–67% yields from acrylates. The acrylamides gave 4-oxobutanamides in 55–56% yields, and 3-sulfonylaldehydes could be obtained from vinyl sulfones in excellent 84% yield. 4-Ketoaldehydes could be obtained from various α,β-unsaturated ketones smoothly in 61–75% yields. The molecular dynamics studies revealed that the formyl radicals arise from the concerted chlorine and hydrogen atom elimination.



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Related Reagents. Carbon Monoxide; Formaldehyde; Formic Acid.

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Dan Liu and Yiyun Chen
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China

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