# Reaction of 2-Halo-1-Olefin-1-Carboxylic Acid with $Cu_2O$ and Isonitrile

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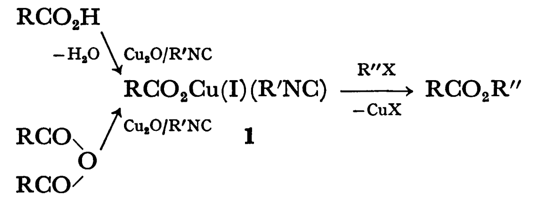
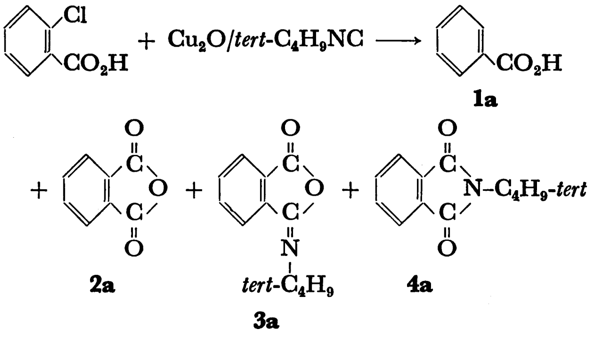
A reaction of 2-halo-1-olefin-1-carboxylic acids with isonitrile and $Cu_2O$ is described. *o*-Chlorobenzoic acid is treated with *tert*-butyl isocyanide and $Cu_2O$ at 80 °C to produce benzoic acid (**1a**), phthalic anhydride (**2a**), *N*-*tert*-butylphthalisoimide (**3a**) and *N*-*tert*-butylphthalimide (**4a**) in 5, 14, 18, and 32% yields, respectively. With 2-chloro-1-cyclohexene-1-carboxylic acid, a similar result is observed. However, the reaction of acyclic 2-chloro-1-olefin-1-carboxylic acid such as *β*-chlorocrotonic acid with isonitrile and $Cu_2O$ does not give any products corresponding to **1**—**4**. These reactions are interestingly compared with the reaction of *o*-iodobenzoic acid and copper(I) acetylide producing 3-alkylidenephthalide. A reaction mechanism involving a transient intermediate of *α*,*β*-unsaturated *β*-lactone (**11**) is proposed for the present reaction.

In the preceeding papers, we have reported that carboxylic acid[1)] and carboxylic acid anhydride[2)] are readily esterified with alkyl halides in the presence of $Cu_2O$/Isonitrile complex. For this esterification, a reaction mechanism has been established in which Cu(I) carboxylate isonitrile complex (**1**) was initially generated by the reaction of $Cu_2O$/Isonitrile complex with carboxylic acid or with carboxylic acid anhydride, and then **1** reacted with alkyl halides to produce the corresponding carboxylic esters. Aromatic halides could not react with **1**.



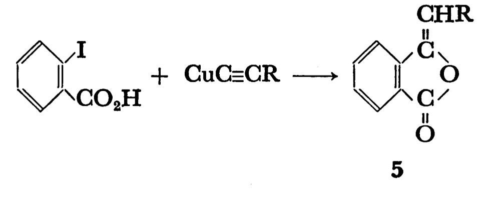
$$RCO_2Cu(I)(R'NC) \xrightarrow[-CuX]{R''X} RCO_2R'' \qquad (1)$$

Now, we found that *o*-chlorobenzoic acid reacted with $Cu_2O$/*tert*-butyl isocyanide complex to give the following products, **1a**, **2a**, **3a**, and **4a**.



(2)

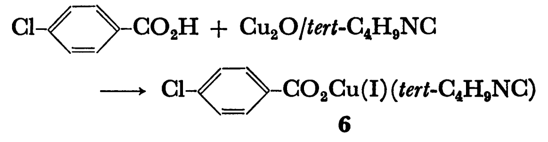
Similar reactions were observed with 2-chloro-1-cyclohexene-1-carboxylic acid and 2-chloro-1-cyclopentene-1-carboxylic acid. These reactions are interestingly compared with the following reaction reported by Castro *et al.*, *i.e.*, the reaction of *o*-iodobenzoic acid and copper(I) acetylide producing 3-alkylidenephthalide.[3)]



(3)

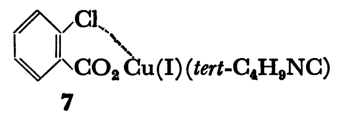
## Results and Discussion

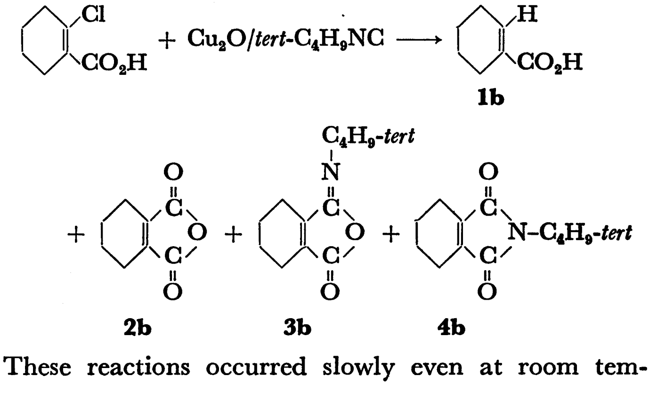
On heating a mixture of *p*-chlorobenzoic acid, $Cu_2O$ and *tert*-butyl isocyanide in benzene at 80 °C for 12 hr under nitrogen, Cu(I) *p*-chlorobenzoate (*tert*-butyl isocyanide) complex (**6**) was only produced in an almost quantitative yield.[1)]



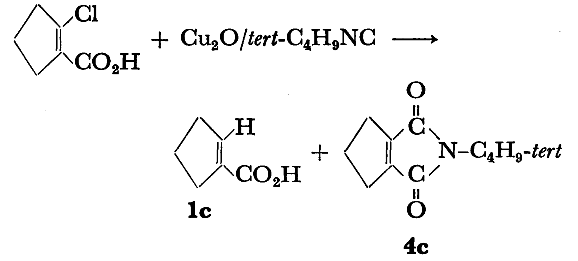
(4)

However, the reaction of *o*-chlorobenzoic acid with $Cu_2O$/*tert*-butyl isocyanide was quite different from that of *p*-chlorobenzoic acid. Four products **1a**, **2a**, **3a**, and **4a** were isolated by glpc in 5, 14, 18, and 32% yields, respectively. Products **2a** and **4a** appear to have been derived by the hydrolysis and rearrangement of **3a**, respectively. The rearrangement of isoimide **3** to imide **4** has been documented in a literature.[4)] The remarkable difference of reactivity between the *ortho*- and the *para*-isomers strongly suggests that Cu(I) *o*-chlorobenzoate (*tert*-butyl isocyanide) complex (**7**) is stabilized by chelation with chlorine in the *ortho* position to the carboxyl group. With 2-chloro-1-cyclohexene-1-carboxylic acid, which is considered to have an analogous geometrical circumstance, a similar result was observed. Four products, **1b**, **2b**, **3b**, and **4b** were isolated in 5, 13, 20, and 41% yields, respectively.



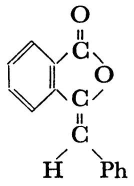


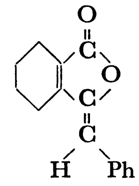
These reactions occurred slowly even at room temperature. For instance, in the reaction of 2-chloro-1-cyclohexene-1-carboxylic acid with $Cu_2O$/*tert*-butyl isocyanide at 20 °C for 70 hr, **1b**, **2b**, **3b**, and **4b** were produced in 1, 2, 32, and 5% yields, respectively. Also, the reaction of 2-chloro-1-cyclopentene-1-carboxylic acid with $Cu_2O$/*tert*-butyl isocyanide at 80 °C produced **1c** and **4c** but in low yields.



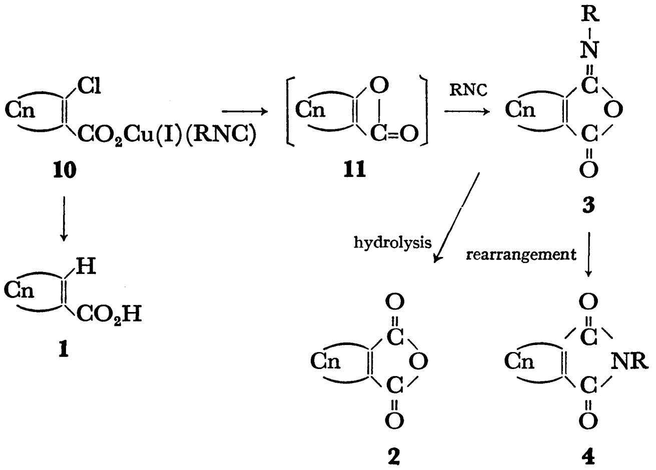
However, the reaction of acyclic 2-chloro-1-olefin-1-carboxylic acid such as *β*-chlorocrotonic acid with $Cu_2O$/isonitrile did not give any product corresponding to **1**—**4**.

The treatment of *o*-bromobenzoic acid with a mixture of *tert*-butyl isocyanide and phenylacetylene in the presence of $Cu_2O$ in pyridine solvent afforded a major product of 3-benzylidenephthalide (**8**, 53%) as reported by Castro *et al.*,[3] and by-products of **1a**, **3a**, and **4a**.

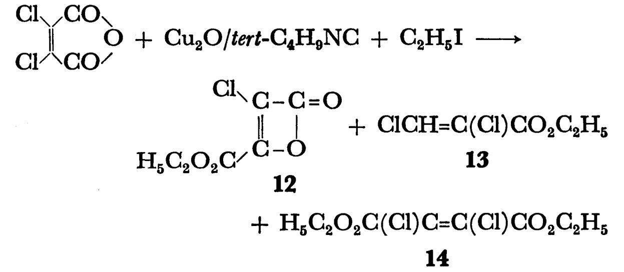

**8**


**9**

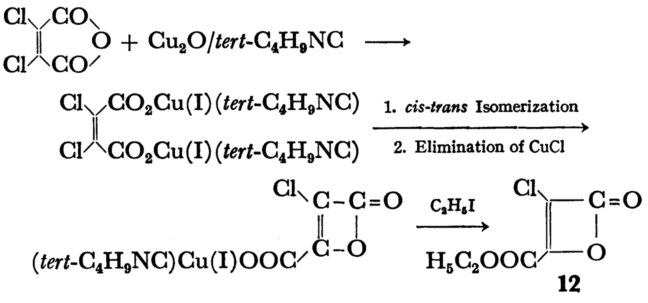
Similarly, 2-chloro-1-cyclohexene-1-carboxylic acid reacted with a mixture of *tert*-butyl isocyanide and phenylacetylene to produce **9** (70%) with **2b**, **3b**, and **4b**. The following scheme may possibly proposed for the reaction of $Cu_2O$/isonitrile with 2-halo-1-cyclic olefin-1-carboxylic acid, which involves a transient intermediate of **11**.



Intramolecular elimination of CuCl from **10** leading to lactone **11** is followed by the reaction with isonitrile. It is also conceibable that the elimination of CuCl from **10** and the reaction of **11** with isonitrile occur synchronously. The formation of **1** is understandable from the fact that aromatic halide is readily reduced by a system of $Cu_2O$–pyridine–acetic acid.[5] Concerning the intermediate of **11**, it may be pertinent to mention the following reaction. A reaction of dichloromaleic anhydride with $Cu_2O$/*tert*-butyl isocyanide in the presence of ethyl iodide afforded **12** in 42% yield along with **13** (5%) and **14** (10%).



The structure of **12** was established by IR, elemental analysis and its chemical reaction (see Experimental Section). The formation of **12** will be reasonably explained by a scheme shown below.



## Experimental

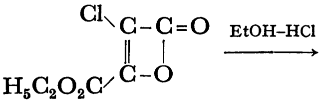
*Reaction of* o-*Chlorobenzoic Acid with* $Cu_2O$/tert-*Butyl Isocyanide*. A mixture of 3.4 g (20 mmol) of *o*-chlorobenzoic acid, 1.43 g (10 mmol) of $Cu_2O$ and 1.66 g (20 mmol) of *tert*-butyl isocyanide in 10 ml of benzene was heated at 80 °C for 20 hr with stirring under nitrogen. The reaction mixture was treated with 10 ml of petroleum ether to remove Cu(I)Cl-(*tert*-butyl isocyanide) complex, and filtered. The filtrate was concentrated *in vacuo*, and subjected to glpc analysis. Four products **1a**, **2a**, **3a**, and **4a** were isolated. The structures of **1a** and of **2a** were established by comparison of IR spectra with the respective authentic samples. Structures of **3a** and **4a** were determined by IR, NMR, and elemental analysis. **3a**: Found: C, 69.93; H, 6.36; N, 6.94%. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89%. IR ($cm^{-1}$): 1850, 1820, 1780, 1710. NMR ($CDCl_3$ with TMS): 1.48 (s, 9H), 7.70 (s, 4H). **4a**: Found: C, 70.69; H, 6.28; N, 6.91%. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89%. Mass $M^+=203$. IR ($cm^{-1}$): 1778, 1712. NMR ($CDCl_3$ with TMS): 1.68 (s, 9H), 7.71 (s, 4H).

*Reaction of 2-Chloro-1-cyclohexene-1-carboxylic Acid with* $Cu_2O$/tert-*Butyl Isocyanide*. According to the procedure described above, a mixture of 1.60 g (10 mmol) of 2-chloro-1-cyclohexene-1-carboxylic acid, 0.72 (5 mmol) of $Cu_2O$ and 0.83 (10 mmol) of *tert*-butyl isocyanide in 5 ml of benzene was reacted at 80 °C for 30 hr. Products **1b**, **2b**, **3b**, and **4b** were isolated by glpc. The structures of **1b** and **2b** were confirmed by comparison of their IR spectra with those of the authentic samples. Structures of **3b** and **4b** were determined by IR, NMR, and elemental analysis. **3b** (mp 75—77 °C): Found: C, 69.26; H, 8.29; N, 6.62%. Calcd for

$C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%. IR ($cm^{-1}$): 1810, 1775, 1690. NMR ($CDCl_3$ with TMS): 1.34 (s, 9H), 1.72 (m, 4H), 2.32 (m, 4H). **4b** (mp 66 °C): Found: C, 69.40; H, 8.22; N, 6.84%. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%. IR ($cm^{-1}$): 1770, 1710. NMR ($CDCl_3$ with TMS): 1.53 (s, 9H), 1.69 (m, 4H), 2.22 (m, 4H). Similarly, the reaction of 2-chloro-1-cyclopentene-1-carboxylic acid with $Cu_2O$/*tert*-butyl isocyanide was carried out. Among several products, **1c** (5%) and **4c** (2%) were identified. **1c** was identified by comparison with the authentic sample. **4c**: Found: C, 68.52; H, 7.61; N, 7.58%. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%. IR ($cm^{-1}$): 1770, 1710. NMR ($CDCl_3$ with TMS): 1.54 (s, 9H), 2.50 (m, 6H). Mass $M^+=193$.

*Competitive Reaction of 2-Chloro-1-cyclohexene-1-carboxylic Acid with* tert-*Butyl Isocyanide and Phenylacetylene in the Presence of $Cu_2O$ in Pyridine.* A mixture of 2.00 g (13 mmol) of 2-chloro-1-cyclohexene-1-carboxylic acid, 1.01 g (7 mmol) of $Cu_2O$, 1.33 g (13 mmol) of phenylacetylene, and 1.58 g (19 mmol) of *tert*-butyl isocyanide in pyridine (25 ml) was heated at reflux under nitrogen gas for 14 hr. After the reaction mixture was filtered, the filtrate was subjected to fractional distillation *in vacuo*. Products **9**, **2b**, **3b**, and **4b** was isolated by glpc in 4, 23, and 2% yields, respectively. Product **9** (70%) was crystallized from ligroin (mp 118—120 °C); Found: C, 79.26; H, 6.61%. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24%. NMR ($CDCl_3$ with TMS): 1.75 (broad, 4H), 2.40 (broad, 4H), 5.85 (s, 1H), 7.2, 7.8 (m, 5H).

*Reaction of Dichloromaleic Anhydride with $Cu_2O$/*tert*-Butyl Isocyanide in the Presence of Ethyl Iodide.* A mixture of 1.67 g (10 mmol) of dichloromaleic anhydride, 1.43 g (10 mmol) of $Cu_2O$, 1.66 g (20 mmol) of *tert*-butyl isocyanide and 3.12 g (20 mmol) of ethyl iodide was stirred at 80 °C for 10 hr under nitrogen. After the reaction mixture was treated with petroleum ether, and filtered, the filtrate was evaporated. Products **12**, **13**, and **14** was isolated by glpc. Identity of **13** and of **14** was established by comparison of their IR spectra with those of the authentic samples. Structure determination of **12** was performed by IR, NMR, elemental analysis and its chemical reaction. **12**: Found: C, 40.84; H, 2.82; Cl, 20.37%. Calcd for $C_6H_5O_4Cl$: C, 40.81; H, 2.85; Cl, 20.82%. IR ($cm^{-1}$) 1875—1830, 1790, 1750, 1655. Treatment of **12** with HCl saturated ethanol at 80 °C for 2 hr gave two products **15** and **16** in the ratio of 4 to 1.



**12**

$H_5C_3O_2C(Cl)C{=}C(OC_2H_5)CO_2C_2H_5$

**15**

$H_5C_2O_2C(Cl)CH{-}C(OC_2H_5)_2CO_2C_2H_5$

**16**

**15**: Found: C, 48.12; H, 6.09; Cl, 14.05%. Calcd for $C_{10}H_{15}O_5Cl$: C, 47.91; H, 6.03; Cl, 14.14%. IR ($cm^{-1}$): 1741, 1710, 1610. NMR ($CDCl_3$ with TMS): 1.28 (t, 3H), 1.36 (t, 3H), 1.37 (t, 3H), 4.06 (q, 2H), 4.37 (two q, 4H). **16**: Found: C, 48.45; H, 7.20; Cl, 12.02%. Calcd for $C_{12}H_{21}O_6Cl$: C, 48.57; H, 7.13; Cl, 11.95%. IR ($cm^{-1}$): 1760. NMR ($CDCl_3$ with TMS): 1.29 (two t, 6H), 1.33 (t, 3H), 1.39 (t, 3H), 3.75 (two q, 4H), 4.36 (two q, 4H), 4.84 (s, 1H).

## References

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