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The reaction of *N*-carboalkoxy Reissert analogs in the presence of carboxylic acids yields the corresponding ester and heterocyclic base. Use of methoxy substituted benzoic acids yields, instead of the ester, the respective anhydride. Amides can also be prepared in a similar fashion.

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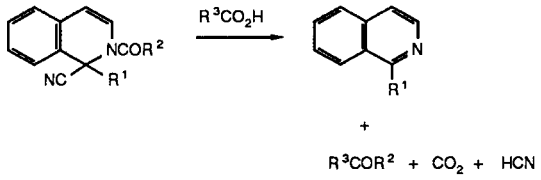
Reissert compounds are known to undergo a variety of different types of reactions [2a,b] and they have been widely used as key intermediates in the synthesis of various heterocyclic compounds.

Recently, Tsizin and co-workers [3] have shown that when the *N*-carboalkoxy Reissert analogs are heated in the presence of carboxylic acids the isolated products were the regenerated heterocyclic base, carbon dioxide, hydrogen cyanide, and the corresponding ester (Scheme I). Until now, this retro-Reissert reaction was reported only by either acid or base hydrolysis [5a]. Tsizins's procedure offers the advantage of milder conditions coupled with offering a synthetic method with some potential applications. We have therefore extended the study of this retro-Reissert reaction (Scheme I) by incorporating the use of other *N*-carboalkoxy and *N,N*-dialkyl (diaryl) carbamoyl Reissert analogs and carboxylic acids.

Scheme I



Using the 2-phenoxycarbonylisoquinoline Reissert analog with benzoic acid it was determined that a molar ratio of one mole of Reissert compound to three moles of benzoic acid gave the highest yields of isolated phenyl benzoate (Table I). The 2-phenoxycarbonylisoquinoline Reissert analog was reacted with variety of carboxylic acids to give esters isolated as summarized in Table II. The yields of the ester isolated varies from 27% for stearic acid to 96% for 4-chlorobenzoic acid. Generally the esters were obtained in high yields. The high yield and simple procedure suggests the feasibility of using this procedure in cases with a compound which may not survive under standard esterification methods. Table III summarizes the yields of ester isolated using the 2-isobutoxy, 2-methoxy, and 2-ethoxycarbonyl Reissert analogs with various carboxylic acids.

Table I

Yields of Phenyl Benzoate from the Reaction of the 2-Phenoxycarbonylisoquinoline Reissert Analog with Benzoic Acid (Scheme I)

R^1 = H, R^2 = OPh, R^3 = Ph

Entry	mole ratio	Ester (% yield)
1	1:1	83
2	1:2	89
3	1:3	92
4	1:4	83

Table II

Yields of Phenyl Esters from the Reaction of the 2-Phenoxycarbonylisoquinoline Reissert Analog in the Presence of Various Acids (Scheme I)

R^1 = H, R^2 = OPh

Entry	R	Ester (% yield)
5	*p*-$CH_3C_6H_4$	93
6	*p*-$CH_3OC_6H_4$	92
7	*p*-ClC_6H_4	96
8	*p*-$O_2NC_6H_4$	67
3	Ph	92
9	$CH_3(CH_2)_{16}$	27
10	*o*-HOC_6H_4	86
11	C_4H_3O (furoic)	86

Although the phenyl ester of 4-methoxybenzoic acid was prepared (Table II) the reaction of 4-methoxybenzoic acid (entry 19) with the 2-methoxycarbonyl Reissert analog did not yield the expected methyl ester, but rather the anhydride of 4-methoxybenzoic acid (Table IV, Scheme II). Both the 3,4- and 3,5-dimethoxybenzoic acids were

Table III

Yields of Ester from the Reaction of the 2-Methoxy, 2-Ethoxy, and 2-Isobutoxycarbonylisoquinoline Reissert Anologs in the Presence of Carboxylic Acids (Scheme I)

	R^1 = H		
Entry	R^2	R^3	Ester (% yield)
12	OMe	p-$O_2NC_6H_4$	86
13	OMe	Ph	55
14	OMe	$CH_3(CH_2)_{16}$	42
15	OEt	p-$O_2NC_6H_4$	27
16	OEt	Ph	95
17	OEt	C_4H_3O (furoic)	85
18	*O-iso*-Butyl	Ph	68

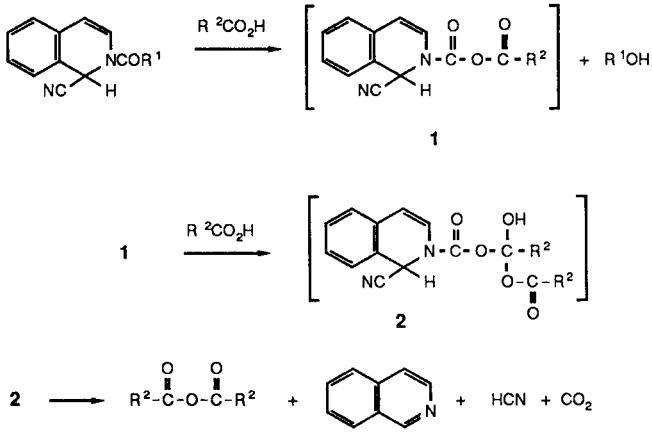
reacted with the 2-methoxycarbonyl Reissert analog yielding, in both cases, the anhydride of the acids (entries 20, 21). The 2-ethoxycarbonyl Reissert analog reacted with both 4-methoxy and 4-methylbenzoic acid (entries 22, 23) to yield not the expected methyl ester but the corresponding anhydrides.

Table IV

Yields of Anhydride from the Reaction of 2-Ethoxy and 2-Methoxycarbonylisoquinoline Reissert Analogs with Substituted Methyl and Methoxy Benzoic Acid (Scheme II)

Entry	R^1	R^2	Anhydride (% yield)
19	Me	4-$MeOC_6H_4$	49
20	Me	3,4-$(MeO)_2C_6H_3$	53
21	Me	3,5-$(MeO)_2C_6H_3$	44
22	Et	4-$MeOC_6H_4$	55
23	Et	4-MeC_6H_4	59

Scheme II



The *N,N*-dialkyl (and diaryl) carbamoyl Reissert analogs reacted with carboxylic acids in a similar fashion as their *N*-carboalkoxy counterparts to give the corresponding disubstituted benzamides (Table V) in 63 to 83% yield (Scheme I). Use of an ester in place of the carboxylic acid did not lead to any amide formation.

Table V

Yields of Benzamides from the Reaction of Carbamoylisoquinoline Reissert Analogs and Benzoic Acid (Scheme I)

	R^3 = Ph		
Entry	R^1	R^2	Amide (% yield)
24	H	$N(Ph)_2$	81
25	H	$N(Et)_2$	63
26	H	$N(Me)_2$	83

Uff and co-workers [4] have also applied this retro-Reissert reaction in their study of benzothiazole and benzimidazole Reissert analogs using both substituted and unsubstituted derivatives. Uff observed that reacting the benzothiazole and benzimidazole Reissert analogs with either hexanoic or benzoic acid yielded both the substituted and unsubstituted aromatic heterocyclic bases in 40-59% yield.

Our study suggests that for the retro-Reissert reaction to proceed the substituent attached to the carbon alpha to the cyano group must not be a large and bulky substituent (Scheme I). These results are summarized in Table VI. The 1-methyl- and 1-ethyl-2-phenoxycarbonyl Reissert compounds gave the 1-substituted isoquinoline in yields compatible to those of Uff's study. However, the benzylated analogs gave either no reaction or very low yields of 1-benzylisoquinoline (entries 30-32).

Table VI

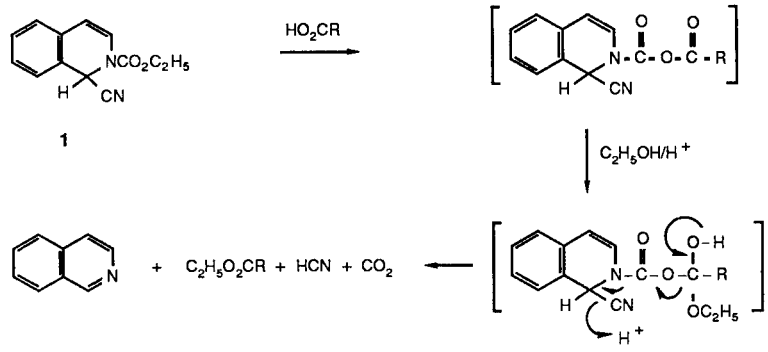
Yields of Aromatic Heterocyclic Base and Ester from the Reaction of Alkylated Isoquinoline Reissert Analogs with Benzoic Acid (Scheme I)

	R^3 = Ph		(% yield)	
Entry	R^1	R^2	base	ester
27	Me	OPh	58	76
28	Et	OPh	36	---- [a]
29	Me	OEt	56	19
30	$PhCH_2$	OPh	NR [c]	NR [c]
31	$PhCH_2$	$N(CH_3)_2$	18	---- [a]
32	$PhCH_2$	$N(Ph)_2$	11	---- [a]
3 [b]	H	OPh	77	92

[a] Not isolated. [b] Entered for comparison purposes. [c] Starting material isolated.

Uff and co-workers [4] have suggested a mechanism by which this retro-Reissert reaction may be occurring (Scheme III). The first step involves the formation of a mixed anhydride intermediate and a corresponding

Scheme III



alcohol. The alcohol may then add to the mixed anhydride intermediate generating a second intermediate which ultimately yields the observed products. Our results suggest that when appropriately activated benzoic acids are used, benzoic anhydride formation becomes competitive with ester formation from **1**, *via* **2** (Scheme II). Although ester formation could be a result of alcoholysis of the benzoic anhydride rather than **1**, the high yield of the ester (86%) observed when a 1:1 mole ratio of substrate to carboxylic acid was used (Table 1) suggests alcoholysis of **1** may be the more usual pathway.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 710B spectrometer. Proton magnetic resonance spectra were determined on a Hitachi Perkin Elmer 12-R-24 B instrument using tetramethylsilane as the reference compound. Microanalysis was performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

Preparation of the Reissert Analogs and Derivatives Derived from Chloroformates.

These compounds were prepared according to the method of Popp *et al.* [5a,b].

Preparation of 1-Cyano-2-isobutoxycarbonyl-1,2-dihydroisoquinoline.

To a mixture of 2.5 g (19.5 mmoles) of isoquinoline in 60 ml of methylene chloride and 3.90 ml (29.2 mmoles) trimethylsilylcyanide was added 3.80 ml (29.2 mmoles) of isobutylchloroformate over a one hour period. Following stirring overnight the mixture was washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide, water and dried over anhydrous magnesium sulfate. Concentration of the methylene chloride afforded 4.96 g (99%) of the titled compound which was purified further on 60-200 mesh silica gel with chloroform; ir (thin film): 1706 cm^{-1} (C=O); pmr (deuteriochloroform): 7.15 ppm (s, 4H), 6.80 ppm (d, 1H), 6.22 (s, 1H), 5.90 (d, 1H), 4.00 ppm (d, 2H), 2.00 ppm (m, 1H), 1.00 ppm (d, 6H).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 70.29; H, 6.29. Found: C, 70.09; H, 6.31.

Reactions of the Reissert Analogs with Carboxylic Acids.

General Procedure.

The Reissert compound and the respective acid (1:3 molar ratio) were placed into a reaction vessel fabricated to fit onto a Claisen head. The Claisen head was attached to a 250 ml round bottom flask. The temperature of the reaction vessel was maintained at 135° by means of refluxing *p*-xylene. After a reaction time of 2.5 hours the reaction mass was allowed to cool and then diluted with methylene chloride (90-100 ml). The methylene chloride was then washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide, brine and dried over anhydrous magnesium sulfate. Concentration of the methylene chloride afforded the ester. All solid esters were recrystallized to a constant melting point. Liquid esters were purified by chromatography (60-200 mesh silica gel) using chloroform as the elutant. The heterocyclic base was isolated by neutralizing the acid wash with sodium hydroxide followed by extracting the aqueous solution with (2 x 50 ml) methylene chloride. The methylene chloride was dried over anhydrous magnesium sulfate and removed *in vacuo*. All nmr and ir spectroscopic data were consistent with structure of isolated products.

REFERENCES AND NOTES

[1] Part LVII of the series on Reissert Compound Studies by F. D. Popp and part **19** of studies with Reissert Compounds by B. C. Uff. The previous part in both series is B. C. Uff, Y. P. Ho, D. L. W. Burford and F. D. Popp, *J. Heterocyclic Chem.*, **24**, 1349 (1987).

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