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Exploring the Synthetic Versatility of the Lewis Acid Induced Decomposition Reaction of α-Diazo-β-hydroxy Esters. The Case of Ethyl Diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate

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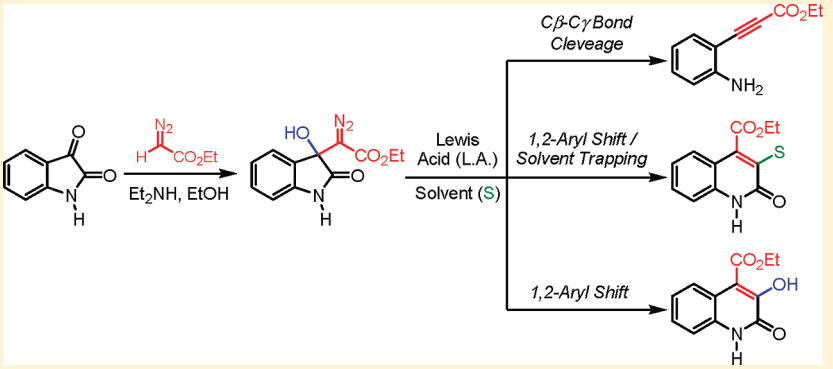
Supporting Information

ABSTRACT:



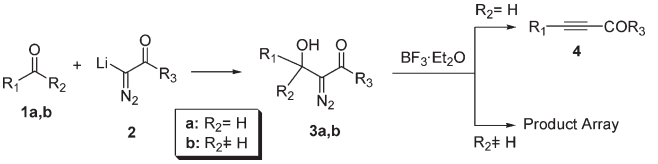
Ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate was prepared by aldol-type condensation of ethyl diazoacetate with isatin. A systematic and mechanistic study on the Lewis acid induced decomposition reaction of this valuable diazo precursor was carried out with the aim to gain new insights into the mechanistic aspects of the reaction as well as to further understand the factors and experimental conditions which affect the relative product distribution. The reaction, which may proceed via cationic and noncationic mechanisms, was found to be significantly influenced by the reaction environment determined by the characteristics of the Lewis acid employed, by the ability of the Lewis acid to form a complex with the alcohol functionality of the α-diazo-β-hydroxy ester, and by the polarity and nucleophilicity of the solvent used.

INTRODUCTION

One of the main challenges for synthetic chemists is related to the development and implementation of efficient methodologies for the preparation of complex scaffolds and intermediates of biologically relevant compounds. Among the chemical transformations that exemplify innovative and flexible methods, the Lewis acid promoted reaction of α-diazo esters has attracted great attention because of their wide range of synthetic applications in both organic and medicinal chemistry.[1]

In this framework, we have investigated the potentiality associated with the use of α-diazo-β-hydroxy esters as synthetic precursors and defined the structural and experimental parameters which influence product types and ratios.[2] An important contribution to the development of synthetically useful reactions came from the employment of boron trifluoride etherate ($BF_3 \cdot OEt_2$) as the Lewis acid. We have shown, in particular, that the reaction of $BF_3 \cdot OEt_2$ with α-diazo-β-hydroxy esters **3a**, **b** generated a variety of products as the result of carbenium ion rearrangement and solvent trapping (Scheme 1).[2b,c] Thus, the reaction of acyclic compounds of type **3a** (R_2 = H) with $BF_3 \cdot OEt_2$ in a polar solvent such as acetonitrile furnished the corresponding acylacetylene derivatives **4** in good yield.[3] This procedure, which proceeds by the extrusion of molecular nitrogen, was successfully applied to the synthesis of biologically active terpenes.[3]

Scheme 1. General Scheme for $BF_3 \cdot OEt_2$-Induced Decomposition of α-Diazo-β-hydroxy Esters 3a,b



Notably, exposure to $BF_3 \cdot OEt_2$ of α-diazo-β-hydroxycarbonyl compounds derived from ketones **3b** was shown to afford an array of diverse products (Scheme 1). In particular, using acetonitrile as the solvent of the reaction, α- and β-enamino esters were obtained as the final compounds with diverse

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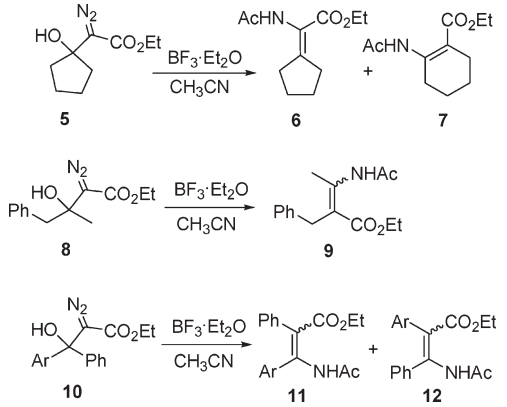
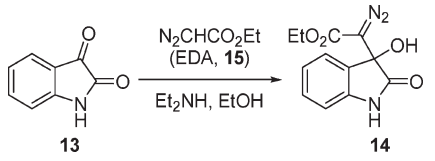
Scheme 2. $BF_3 \cdot OEt_2$-Induced Decomposition of α-Diazo-β-hydroxy Esters 5, 8, and 10 in Acetonitrile



Scheme 3. Synthesis of Ethyl Diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (14)



regioselectivity. For instance, the treatment of ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate (**5**) with freshly distilled $BF_3 \cdot OEt_2$ in acetonitrile gave the α-acetylamino-cyclopentylidenyl carboxylate **6** and β-acetylamino-cyclohexenyl carboxylate **7** in 55% and 6% yields, respectively.[2b] Moreover, the reaction of acyclic α-diazo-β-hydroxyacyl methanes **8** and **10** with $BF_3 \cdot OEt_2$ in acetonitrile afforded β-enamine derivatives **9**, **11**, and **12** as the major products in good yields (Scheme 2).[2b,c]

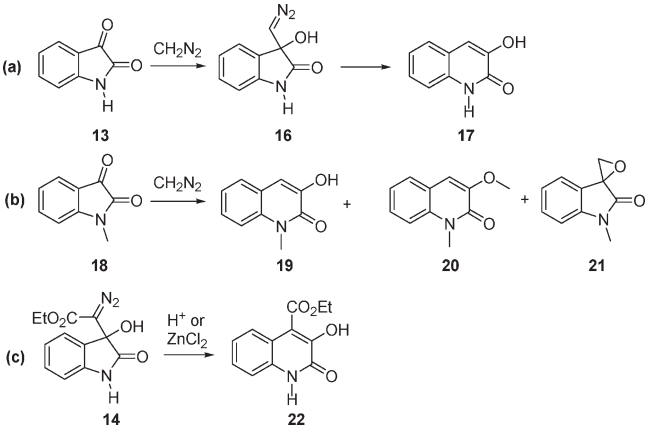
These results have not only been instrumental for the development of new synthetic methodologies but have also provided new insights into the mechanistic aspects of the reaction as well as a further understanding of the factors and experimental conditions which govern the product formation and their relative distribution. As an expansion of the aim and applications of this reaction, herein we report a detailed investigation on experimental parameters along with a survey of the reaction scope with respect to ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**), prepared from the reaction of isatin (**13**) with ethyl diazoacetate (EDA, **15**) in the presence of Et_2NH (Scheme 3).[8b]

BACKGROUND

Isatin (**13**) and its derivatives are synthetically useful substrates for the preparation of several heterocyclic compounds endowed with biological and pharmacological interest.[4] The presence of several reaction centers makes them suitable for various types of reactions, including reduction and oxidation of the heterocyclic ring, nucleophilic addition at the C-3 position, nucleophilic substitution at the C-2 position, and N-alkylation and -acylation, as well as Mannich and Michael reactions and benzene electrophilic substitutions.

Among C-3 nucleophilic additions, it was shown that the reaction of isatin (**13**) with diazoalkanes, such as diazomethane[5]

Scheme 4. Reactions of Isatin Derivatives with Diazomethane and Ethyl Diazoacetate



and diazoarylalkanes,[6] furnished 2-quinolinones by ring expansion of the diazo carbinol intermediate **16** (Scheme 4a). In a later study, Kennewell and co-workers observed different results using 2-alkyloxyindol-3-ones as starting materials.[7] In particular, they found that *N*-methylisatin (**18**) reacted with a slight excess (1.07 equiv) of diazomethane to produce hydroxyquinoline **19** in 74% yield. On the other hand, when an excess of diazomethane was used, the epoxide **21** was isolated along with 2-quinolinones **19** and **20** (Scheme 4b). Rather less investigated are the C-3 additions of diazo carbonyl compounds. The few examples reported by Eistert concerned the reaction of ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**) with hydrochloric acid (or a catalytic amount of zinc chloride) to afford ethyl 3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (**22**), in 86% yield (Scheme 4c).[8]

Despite the great potential of this approach in the preparation of 2-quinolinone derivatives, to date its employment is quite limited and has been scarcely explored. Since the mechanism proposed for this process involves a vinyl cation intermediate, we decided to extend the understanding of the decomposition pathways of ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**) as well as to further demonstrate its synthetic versatility. The effects of both Lewis acid and solvent in the product distribution, as well as the mechanistic aspects of the reactions, are herein described.

RESULTS AND DISCUSSION

Ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**) was prepared as previously described (Scheme 3).[8b] Initially, we examined the $BF_3 \cdot Et_2O$-promoted decomposition reaction of **14** in acetonitrile. Thus, a solution of **14** (3.7×10^{-2} M in acetonitrile) was added by syringe pump (0.02 mmol/min) to an acetonitrile solution of $BF_3 \cdot Et_2O$ (1.5 equiv), at room temperature, to furnish three compounds in a 4:40:56 ratio, as evidenced by HPLC analysis of the crude reaction mixture (Table 1, entry a). The products were purified by silica gel flash chromatography and characterized by mono- and bidimensional NMR spectroscopy. In addition to ethyl 3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (**22**) and ethyl 3-acetylamino-2-oxo-1,2-dihydroquinoline-4-carboxylate (**23a**), obtained in 2% and 40% yields, respectively, the unexpected ethyl (2-aminophenyl)propynoate (**24**)[9] was formed as the major product of the reaction in 51% yield.

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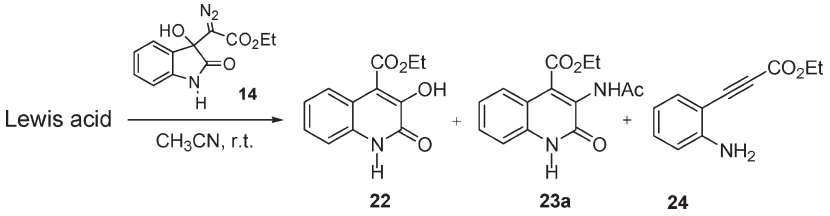
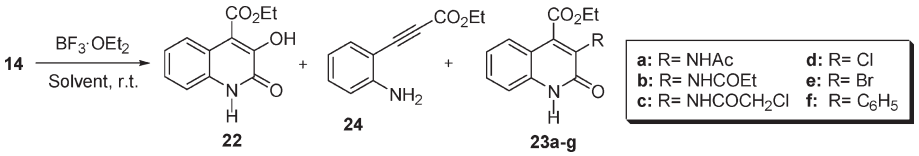
Table 1. Decomposition of Ethyl Diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (14) with Different Lewis Acids[a]



entry	Lewis acid	product ratio (%)[b] **22**:**23a**:**24**
a	$BF_3 \cdot Et_2O$	4:40:56
b	$SnCl_2$	100:0:0
c	$Mg(ClO_4)_2$	100:0:0
d	$Zn(OTf)_2$	100:0:0
e	$ZnCl_2$	100:0:0
f	$ZnBr_2$	100:0:0
g	$InBr_3$	99:0.5:0.5
h	$InCl_3$	95:3:2
i	$In(OTf)_3$	82:9:9
l	$Yt(OTf)_3$	65:17:18
m	$Al(OTf)_3$	43:26:31
n	$Sc(OTf)_3$	39:28:33
o	$SnCl_4$	0:40:60

[a] Conditions: solvent CH_3CN, addition rate 0.02 mmol/min. [b] Ratios determined by HPLC analysis of the crude reaction mixture.

Table 2. $BF_3 \cdot Et_2O$-Promoted Decomposition of Ethyl Diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (14) in Various Solvents[a]



entry	solvent	products (amt (%))[b]	isolated products (amt (%))[c]
a	CH_3CN	**22** (4), **23a** (40), **24** (56)	**23a** (40), **24** (51)
b	CH_3CH_2CN	**22** (5), **23b** (37), **24** (58)	**23b** (38), **24** (39)
c	$ClCH_2CN$	**22** (4), **23c** + **23d** (44), **24** (52)	**23c** (34), **23d** (9), **24** (42)
d	CH_2Cl_2	**22** (34), **23d** (24), **24** (52)	**23d** (15), **24** (40)
e	CH_2Br_2	**22** (52), **23e** (14), **24** (33)	**23e** (12), **24** (20)
f	C_6H_6	**22** (58), **23f** (10), **24** (23), **25** (9)	**23f** (8), **24** (26), **25** (3)
g	MeOH	**22** (100)	

[a] Conditions: 1.5 equiv of $BF_3 \cdot Et_2O$, addition rate 0.02 mmol/min. [b] Determined by RP-HPLC analysis of the crude reaction mixture. [c] Isolated yield after flash chromatography; **22** was not isolated.

It should be noted, in this regard, that the product ratio was strongly dependent on the experimental protocol used. As an example, when $BF_3 \cdot Et_2O$ was added to an acetonitrile solution of **14**, the reaction afforded the quinolinone derivative **22** as the sole product of decomposition (97% HPLC yield), following a mechanism similar to the Lewis acid (catalytic) induced decomposition reaction.[8]

The reaction was then repeated in the presence of different Lewis acids (Table 1). Various trends could be discerned according to the Lewis acid employed. In particular, in the presence of stoichiometric amounts of $SnCl_2$, $Mg(ClO_4)_2$, $Zn(OTf)_2$, $ZnCl_2$, and $ZnBr_2$, the reaction furnished quantitatively the β-enol ester **22** (Table 1, entries b—f), which was the main product of the reaction also with $InBr_3$, $InCl_3$, $In(OTf)_3$, and $Yt(OTf)_3$ (Table 1, entries g—l). In the case of $Al(OTf)_3$ and $Sc(OTf)_3$ catalysis (Table 1, entries m and n), although **22** was still the main product, **23a** and **24** notably increased, while with the use of $SnCl_4$, **22** was absent and only the two products **23a** and **24** were formed (Table 1, entry o).

Subsequently, $BF_3 \cdot Et_2O$ was selected to investigate the effect of different reaction solvents (Table 2). As previously observed in the case of acetonitrile (Table 2, entry a), the reaction of **14** in polar solvents, such as propionitrile and chloroacetonitrile, results in the formation of the acetylene derivative **24** as the

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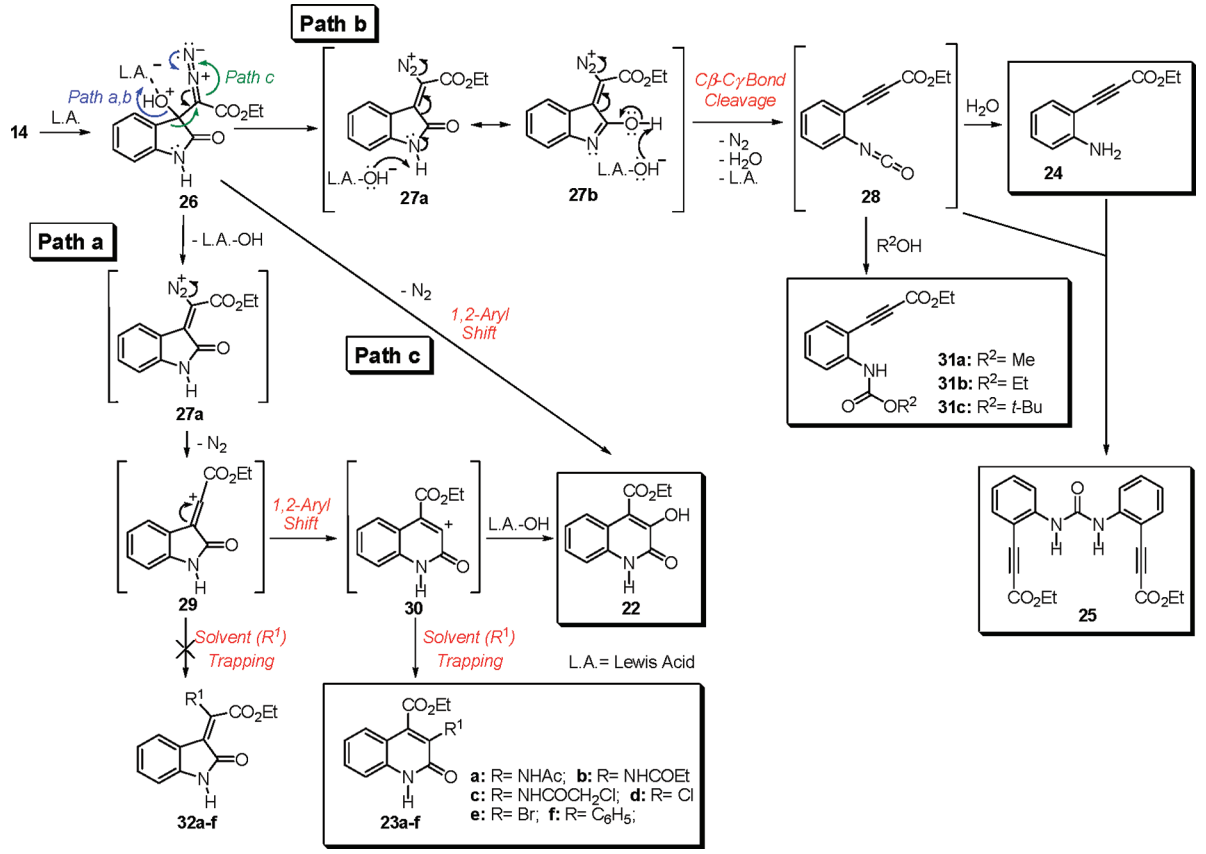
Scheme 5. Proposed Mechanism for Ethyl Diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (14) Decomposition Reactions



major product together with the corresponding solvent-addition products **23b,c** and minor amounts of **22** (Table 2, entries b and c). Unexpectedly, by using chloroacetonitrile, ethyl 3-chloro-2-oxo-1,2-dihydroquinoline-4-carboxylate **23d** was also obtained in 9% yield after silica gel flash chromatography.[10] Likewise, **23d** was obtained along with the acetylene **24** and the β-enol ester **22**, when the reaction was performed in dichloromethane (Table 2, entry d). However, with a variation in product ratio, a mixture of three compounds was obtained by using dibromomethane as solvent (Table 2, entry e). In this case, the compound derived from bromine addition, **23e**, was isolated in 12% yield. Exposure of **14** to $BF_3 \cdot Et_2O$ in benzene afforded a mixture of four components, including the β-enol ester **22** and the propynoate **24** as the main products (Table 2, entry f). The two new minor compounds were characterized, after isolation by flash chromatography, as the expected ethyl 3-phenyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (**23f**, 8% yield) and the unexpected symmetric urea derivative **25** (Scheme 5), whose structure was unambiguously determined by HRMS and NMR analysis. Finally, the decomposition reaction of **14** in methanol gave ethyl 3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (**22**) as the single product (Table 2, entry g).

Reaction Mechanism and Possible Role of Lewis Acid and Solvent. The results reported in Table 1 suggest that the decomposition reaction of ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**) can follow both cationic and noncationic mechanisms according to the Lewis acid employed.

In particular, analogously to our previous reports,[2b,c] in the case of "hard" Lewis acids such as $BF_3 \cdot Et_2O$ and $SnCl_4$ (Table 1, entries a and o), a cationic cascade mechanism which nicely accommodates the products formed can be proposed (Scheme 5). The first step of the reaction consists of the complexation of the hydroxy group of the α-diazo-β-hydroxy ester **14** with the Lewis acid, followed by the generation of the diazonium salt **27a** (Scheme 5, path a). The loss of nitrogen produces the highly destabilized linear vinyl cation **29**, which apparently was not trapped by the solvent. Instead, ring expansion of the cation **29** via a 1,2-aryl shift is a fast process and the resulting vinyl cation **30** is trapped by the solvent to afford products **23a**−**g** or, to a lesser extent, by the Lewis acid coordinated hydroxyl group to give the β-enol ester **22** (Scheme 5).

The formation of the acetylene **24** is consistent with path b depicted in Scheme 5. In accord with a recent work,[11] we hypothesize that, as dinitrogen leaves, lone pair donation from the γ-nitrogen atom of **27a** or from the γ-oxygen of **27b** would lead to $C_\beta - C_\gamma$ bond cleavage, resulting in the highly reactive isocyanate **28**, which finally affords the propynoate **24** by water addition/decarboxylation (Scheme 5, path b). To validate this hypothesis, the $BF_3 \cdot Et_2O$-induced decomposition of **14** was quenched with diverse alcohols, including methanol, ethanol, and *tert*-buttl alcohol (Scheme 5). The isolation of ethyl (2-methoxycarbonylaminophenyl)propynoate (**31a**, 46%), ethyl (2-ethoxycarbonylaminophenyl)propynoate (**31b**, 46%), and ethyl (2-*tert*-butoxycarbonylaminophenyl)propynoate (**31c**,[12] 36%) clearly supported the synthetic pathway for **24** formation.

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Table 3. Relation between SdP Values and Solvent Adduct Yields[18]

solvent adduct	yield (%)[a]	solvent	SdP[17]
23c + 23d	44	$ClCH_2CN$	1.024
23a	40	CH_3CN	0.974
23b	37	CH_3CH_2CN	0.888
23d	24	CH_2Cl_2	0.769
23f	10	C_6H_6	0.270

[a] Determined by RP-HPLC analysis of the crude mixture.

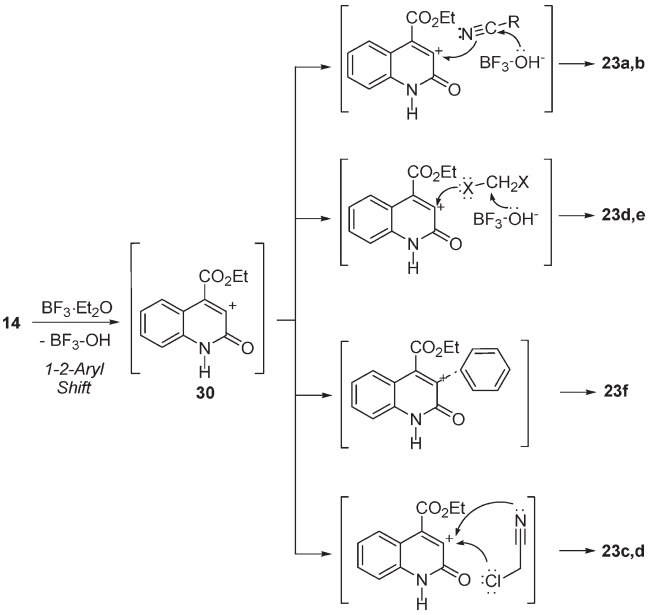
In the case of weaker Lewis acid media (Table 1, entries b−i), the reaction may not go through a cationic process and instead undergoes via concerted 1,2-aryl migration followed by dinitrogen release compound **22** as the only or major product of the reaction (Scheme 5, path c). Thus, when the Lewis acid is moderately strong or the reaction conditions provide a moderately strong Lewis acid environment, the decomposition reaction of **14** furnishes a mixture of **22**, **23a**, and **24** (Table 1, entries l−n).

In addition, although there is no clear logical connection between Lewis acid parameters and the results summarized in Table 1, it can be then assumed that the percentage of the β-enol ester **22** formed in the course of the reaction is inversely proportional to the ability of the Lewis acid to form a stable complex with the hydroxy group of the α-diazo-β-hydroxy ester **14**.[13] Indeed, according to the proposed mechanism depicted in Scheme 5 (path a), $BF_3 \cdot Et_2O$ and $SnCl_4$, which are considered "hard" Lewis acids,[14] are able to remove the hydroxy group from the α-diazo-β-hydroxy ester **14**, resulting in the relatively stable $[LA-OH]^-$. The stability of the complexes, which may correlate with the HSAB principle,[14] favors path b, namely solvent addition and $C_\beta-C_\gamma$ bond cleavage, and hampers the formation of **22**.

In addition to the role played by the Lewis acid, an analysis of the results obtained in Table 2 clearly indicates that the product type and ratio are greatly influenced also by the solvent employed in the decomposition reaction. Several studies have already refined the physical role played by the solvent in the transition-state stabilization of solvolysis reactions.[15] It has been proposed, in particular, that the mechanism for solvolysis of tertiary carbon centers depends on two physically diverse interactions of nucleophilic solvents with the developing carbocation in the transition state: nucleophilic solvent participation (NSP), representing a reaction without a carbocation intermediate, and nucleophilic solvation (NS), which represents transition state stabilization for stepwise solvolysis through carbocation or ion pair intermediates by charge−dipole interactions.[16] According to these considerations, it can be supposed that the solvent parameters which could influence the ratio of the products should be related to the solvent (di)polarity and to the stabilizing interactions between the dipole of the solvent and the vinyl cation **30**. As shown in Table 3, the formation of the solvent adducts **23a**−**f** is favored with higher solvent dipolarity parameter (SdP) values,[17] suggesting that the relative product ratio can be affected by dipolar interactions between **30** and the solvent.

Thus, polar and nucleophilic solvents, such as nitriles, result in a strong stabilization of the vinyl cation **30** and afford **23** as the main product of the reaction, while in contrast, the relatively lower polarity of dichloromethane, dibromomethane, benzene, and anisole favors the reaction of **30** with $[BF_3 \cdot OH]^-$.

Scheme 6. Proposed Mechanism for the Formation of the Solvent Trapping Products



The double site of addition of chloroacetonitrile furnishes the two products of solvent addition **23c,d**, with the percentage probably dependent on the diverse nucleophilic properties of the nitrile group and chlorine atom (Scheme 6). Methanol is not considered here because it follows a different reaction mechanism. Indeed, in the case of methanol, the addition of $BF_3 \cdot Et_2O$ leads first to the formation of $[BF_3 \cdot OMe]^-H^+$, which represents the effective reactant that promotes the decomposition of **14**. Thus, as in the proton-induced decomposition, the reaction in methanol affords the β-enol ester **22** as the exclusive product.[8]

CONCLUSIONS

In conclusion, we have reported a systematic study of the Lewis acid mediated decomposition reaction of ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**) in different solvents. The reaction, which proceeds via cationic and noncationic pathways, leads to a diversity of products according to the Lewis acid and the solvent used. The products and the related mechanism by which they are formed are indeed significantly influenced by several factors: (a) the reaction environment (strong Lewis acid median favors the cationic process), (b) the Lewis acid's ability to form a stable complex with the hydroxy group of **14** (a strong interaction enables the rearrangement of the vinyl cation and the trapping of the solvent), (c) the polarity of the solvent (polar solvents stabilize the rearranged vinyl cation), and (d) the nucleophilicity of the solvent (nucleophilic solvents favor the solvent adduct formation). We think that the decomposition reaction of ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**) represents a rich source of useful intermediates and gives easy access to privileged structures, such as 3-substituted ethyl 2-oxo-1,2-dihydroquinoline-4-carboxylates, structural frameworks of many natural compounds and drugs, as well as ynoate isocyanate, a crucial precursor of *o*-aminophenylpropynoic acid derivatives.

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EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded at 200 and 400 MHz, and ^{13}C NMR spectra were recorded at 100.6 and 50.3 MHz using the solvents indicated below. Chemical shifts are reported in ppm. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets, dddd, doublet of doublets of doublets of doublets, t, triplet, dt, doublet of triplets, qt, quartet of triplets, bs, broad signal. The final products were purified by flash chromatography on silica gel (0.040−0.063 mm). TLC was performed on aluminum-backed silica plates (silica gel 60 F254). All the reactions were performed under a nitrogen atmosphere using distilled solvent. The HPLC analytical-scale experiments were carried out on a LC-Workstation Class LC-10 equipped with a SCL-10 A VP system controller, a LC-10AT VP high-pressure binary gradient delivery system, an SPD-10A VP variable-wavelength UV−vis detector, and a Rheodyne 7725i injector with a 20 μL stainless steel loop. The chromatographic profile was obtained with EZ Start software. All analytical runs were performed by employing a H_2O/MeCN/H_3PO_4 (50/50/0.025 v/v/v) solution as the mobile phase. HPLC-grade water was obtained from a tandem Milli-Ro/Milli-Q apparatus. An Ultra Aqueous C18 250 × 4.6 mm i.d. 5 μm 100 Å analytical column was used after previous conditioning by passing through the column the selected mobile phase for at least 30 min. The UV detection wavelengths were set at 254 and 268 nm. Samples for the analytical-scale analyses were prepared in approximate concentrations between 0.1 and 0.5 mg/mL in filtered mobile phase components and sonicated until completely dissolved. The method EVAL (furnished with the software Enhanced ChemStation Agilent Technology) was used to generate the gradient temperature in the GC-MS analysis.

Ethyl Diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetate (14).[8]. Ethyl diazoacetate (**15**; 42 mL, 360 mmol) and diethylamine (3 mL) were added to a stirred solution of isatin (**3**; 15 g, 120 mmol) in absolute ethanol (400 mL). After 3 days the solvent was evaporated and the crude product was triturated with benzene and filtered to give pure ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**) in 80% yield (25 g; 96 mmol). Compound **14** was obtained as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.4 Hz), 4.15 (m, 2H), 4.75 (brs, 1H), 6.86 (d, 1H, J = 7.8 Hz), 7.01 (t, 1H, J = 7.8 Hz), 7.25 (t, 1H, J = 7.8 Hz), 7.43 (d, 1H, J = 7.8 Hz), 8.39 (br, 1H); ^{13}C NMR 14.1, 61.2, 71.6, 110.9, 123.4, 124.8, 128.6, 130.7, 140.8, 165.3, 177.5.

Caution! Diazo compounds may be explosive and should be handled with care. Storage at −4 °C under an argon atmosphere is strongly recommended.

General Method for Decomposition of 14. *Method A.* A solution of ethyl diazo(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (**14**; 1.11 mmol) in 30 mL of freshly distilled solvent was added at room temperature by syringe pump (0.02 mmol/min) to a magnetically stirred solution of Lewis acid (1.66 mmol) in 5 mL of freshly distilled solvent. At the end of the addition, the reaction mixture was stirred for 30 min at room temperature (quenched with the appropriate alcohol, for the preparation of derivatives **31a**−**c**) and then poured into a saturated solution of $NaHCO_3$ (75 mL), extracted with EtOAc (Table 2, entries 1, 2, 6, and 7) or DCM (Table 2, entries 3 and 4) (3 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography.

Method B. To a magnetically stirred solution of **14** (1.11 mmol) in dry solvent (5 mL) was added a solution of Lewis acid (1.66 mmol) in the same solvent (30 mL) at room temperature with a syringe pump (0.02 mmol/min). After the end of addition the reaction mixture was stirred for 30 min and analyzed by HPLC. The crude reaction product was purified by flash chromatography, furnishing **22** as the sole product of the reaction.

Ethyl 3-Hydroxy-2-oxo-1,2-dihydro-quinoline-4-carboxylate (22):[8] obtained as a pure white solid. Data were consistent with previous literature data.

Ethyl 3-(Acetylamino)-2-oxo-1,2-dihydroquinoline-4-carboxylate (23a): obtained in 40% yield (121 mg, 0.44 mmol) as yellow pure solid; mp 204−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 1.36 (t, 3H, J = 4.6 Hz), 1.39 (t, 3H, J = 7.1 Hz), 4.48 (q, 2H, J = 7.2 Hz), 6.86 (d, 1H, J = 7.8 Hz), 6.94 (dt, 1H, J_d = 0.9 Hz, J_t = 7.7 Hz), 7.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD) δ 13.7, 23.4, 62.8, 106.0, 110.3, 120.3, 120.8, 122.3, 128.3, 137.0, 138.9, 163.2, 168.4, 170.8; GC-MS R_t = 25.784 min, m/z 103 (28), 132 (25), 133 (13), 158 (72), 159 (48), 160 (33), 232 (100), 233 (14), 274 (26); HRMS (+ES) m/z calcd for $C_{14}H_{15}N_2O_4$ 275.1032, found 275.1035.

Ethyl 2-Oxo-3-(propionyloamino)-1,2-dihydroquinoline-4-carboxylate (23b): obtained in 38% yield (120 mg, 0.417 mmol) as yellow pure solid; mp 214−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.5 Hz), 1.45 (t, 3H, J = 7.2 Hz), 2.54 (q, 2H, J = 7.5 Hz), 4.56 (q, 2H, J = 7.2 Hz), 6.92 (d, 1H, J = 7.8 Hz), 7.02 (dt, 1H, J_d = 0.9 Hz, J_t = 7.7 Hz), 7.22 (dt, 1H, J_d = 1.1 Hz, J_t = 7.7 Hz), 7.26 (d, 1H, J = 7.8 Hz), 8.27 (s, 1H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 13.9, 29.9, 62.8, 110.1, 120.7, 121.0, 122.6, 128.1, 137.9, 138.1, 163.2, 170.7, 171.9; GC-MS R_t = 26.466 min, m/z 57 (19), 103 (20), 132 (16), 158 (51), 159 (33), 160 (26), 232 (100), 233 (15), 288 (23); HRMS (+ES) m/z calcd for $C_{15}H_{16}N_2O_4Na$ 311.1008, found 311.1007.

Ethyl 2-Oxo-3-(chloroacetyl)amino-1,2-dihydroquinoline-4-carboxylate (23c): obtained in 34% yield (115 mg, 0.373 mmol) as yellow pure solid; mp 210−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, 3H, J = 7.1 Hz), 4.23 (s, 2H), 4.55 (q, 2H, J = 7.2 Hz), 6.92 (d, 1H, J = 7.8 Hz), 7.04 (dt, 1H, J_d = 1.0 Hz, J_t = 7.7 Hz), 7.24 (dd, 1H, J = 1.1, 7.8 Hz), 7.27 (m, 1H) 7.96 (br s, 1H), 12.48 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 42.2, 63.0, 107.7, 110.2, 120.2, 121.5, 122.7, 128.9, 136.2, 138.6, 162.7, 164.8, 170.2; GC-MS R_t = 27.971 min, m/z 77 (17), 103 (44), 132 (29), 158 (93), 159 (60), 160 (34), 207 (73), 232 (100), 308 (43); HRMS (+ES) m/z calcd for $C_{14}H_{14}N_2O_4Cl$ 309.0642, found 309.0640.

Ethyl 3-Chloro-2-oxo-1,2-dihydroquinoline-4-carboxylate (23d): obtained in 15% (42 mg, 0.166 mmol) and 9% yield (25 mg, 0.10 mmol) as yellow pure solid; mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, 3H, J = 7.1 Hz), 4.50 (q, 2H, J = 7.1 Hz), 6.91 (d, 1H, J_d = 7.8 Hz), 7.00 (dt, 1H, J_d = 0.9 Hz, J_t = 6.8 Hz), 7.30 (dt, 1H, J_d = 1.0 Hz, J_t = 7.7 Hz), 7.44 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 63.3, 110.2, 120.1, 122.4, 123.8, 126.4, 128.8, 131.3, 140.1, 163.2, 166.7; GC-MS R_t = 23.880 min, m/z 89 (20), 114 (31), 116 (24), 125 (10), 144 (99), 150 (69), 152 (22), 170 (59), 172 (19), 179 (57), 181 (17), 188 (21), 206 (37), 251 (100), 253 (35); HRMS (+ES) m/z calcd for $C_{12}H_{11}NO_3Cl$ 252.0427, found 252.0420.

Ethyl 3-Bromo-2-oxo-1,2-dihydroquinoline-4-carboxylate (23e): obtained in 12% yield (39 mg, 0.133 mmol) as yellow pure solid; mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, 3H, J = 7.1 Hz), 4.50 (q, 2H, J = 7.1 Hz), 6.90 (psdt, 1H, J_t = 0.7 Hz, J_d = 7.7 Hz), 7.00 (dt, 1H, J_d = 1.0 Hz, J_t = 7.8 Hz), 7.32 (m, 2H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 63.2, 110.1, 117.8, 120.8, 122.5, 123.3, 127.5, 131.2, 139.5, 164.2, 166.5; GC-MS R_t = 23.707 min, m/z 62 (22), 88 (42), 116 (64), 144 (82), 170 (91), 172 (100), 194 (41), 196 (38), 223 (23), 225 (22), 250 (28), 252 (28), 295 (85), 297 (87); HRMS (+ES) m/z calcd for $C_{12}H_{11}NO_3Br$ 295.9922, found 295.9929.

Ethyl 2-Oxo-3-phenyl-1,2-dihydroquinoline-4-carboxylate (23f): obtained in 8% yield (26 mg, 0.089 mmol) as yellow-orange pure solid; mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 3H, J = 7.1 Hz), 4.44 (q, 2H, J = 7.2 Hz), 6.79 (d, 1H, J = 7.8 Hz), 7.00 (dt, 1H, J_d = 0.9 Hz, J_t = 7.7 Hz), 7.25 (dd, 1H, J = 1.0, 7.7 Hz), 7.35 (d, 1H, J = 7.7 Hz), 7.43 (m, 3H), 7.54 (m, 2H), 7.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 62.2, 109.8, 122.2, 123.1, 124.8, 128.2, 128.7, 129.5, 130.5, 140.9, 167.2, 167.7; GC-MS R_t = 27.247 min, m/z 165 (43), 190 (15), 191 (18), 207 (19), 220 (100), 221 (28), 248 (15), 264 (16), 292 (17),

293 (81), 294 (19); HRMS (+ES) *m/z* calcd for $C_{18}H_{16}NO_3$ 294.1130, found 294.1121.

Ethyl 3-(2-Aminophenyl)-2-propynoate (24):[9] obtained as yellowish pure amorphous solid; see Tables 1 and 2 for the corresponding yields; mp 55−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 1.44(t, 3H, J = 7.1 Hz), 4.23 (br s, 1H), 4.55 (q, 2H, J = 7.2 Hz), 6.95 (t, 1H, J = 7.6 Hz), 7.36 (dt, 1H, J_d = 1.4 Hz, J_t = 8.6 Hz), 7.45 (d, 1H, J = 7.7 Hz), 8.14 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD) δ 13.6, 29.3, 47.9, 48.1, 48.3, 48.5, 48.7, 48.9, 49.1, 63.3, 83.3, 85.7, 108.5, 120.5, 122.5, 131.8, 133.7, 142.0, 152.6, 154.6; GC-MS R_t = 18.950 min, *m/z* 63 (22), 89 (53), 90 (21), 115 (56), 116 (25), 117 (100), 143 (30), 144 (50), 189 (64); HRMS (+ES) *m/z* calcd for $C_{11}H_{11}NO_2Na$ 212.0687, found 212.0682.

Diethyl 3,3′-[Carbonylbis(imino-2,1-phenylene)]bis(prop-2-ynoate) (25): obtained in 3% yield (13 mg, 0.032 mmol) as pure white solid; mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 1.44 (t, 3H, J = 7.1 Hz), 4.23 (br s, 1H), 4.55 (q, 2H, J = 7.2 Hz), 6.95 (t, 1H, J = 7.6 Hz), 7.36 (dt, 1H, J_d = 1.4 Hz, J_t = 8.6 Hz), 7.45 (d, 1H, J = 7.7 Hz), 8.14 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD) δ 13.6, 29.3, 47.9, 48.1, 48.3, 48.5, 48.7, 48.9, 49.1, 63.3, 83.3, 85.7, 108.5, 120.5, 122.5, 131.8, 133.7, 142.0, 152.6, 154.6; GC-MS R_t = 18.950 min, *m/z* 63 (22), 89 (53), 90 (21), 115 (56), 116 (25), 117 (100), 143 (30), 144 (50), 189 (64); HRMS (+ES) *m/z* calcd for $C_{23}H_{21}N_2O_5$ 405.1450, found 405.1444.

Ethyl 3-2-{[(Methoxycarbonyl)amino]phenyl}prop-2-ynoate (31a): obtained in 46% yield (125 mg, 0.51 mmol) as colorless solid; mp 71−73 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (t, 3H, J = 7.1 Hz), 3.85 (s, 3H) 4.36 (q, 2H, J = 7.4 Hz), 7.07 (dt, 1H, J_d = 1.1 Hz, J_t = 7.6 Hz), 7.37 (s, 1H), 7.53 (m, 2H), 8.23 (d, 1H, J = 9.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 52.6, 62.3, 81.2, 87.4, 107.6, 118.1, 122.7, 132.3, 133.4, 140.9, 153.5; GC-MS R_t = 21.943 min, *m/z* 89 (14), 115 (24), 130 (19), 143 (100), 170 (67), 175 (39), 215 (20), 247 (28); HRMS (+ES) *m/z* calcd for $C_{13}H_{14}NO_4$ 248.0923, found 248.0926.

Ethyl 3-2-{[(Ethoxycarbonyl)amino]phenyl}prop-2-ynoate (31b): obtained in 46% yield (109 mg, 0.51 mmol) as colorless pure oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3H, J = 7.1 Hz), 1.38 (t, 3H, J = 6.2 Hz), 4.27 (q, 2H, J = 7.2 Hz), 4.33 (q, 2H, J = 7.1 Hz), 7.04 (dt, 1H, J_d = 1.0 Hz, J_t = 7.6 Hz), 7.46 (dt, 1H, J_d = 1.0 Hz, J_t = 7.6 Hz), 7.52 (dd, 1H, J = 1.1, 7.7 Hz), 8.21 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.5, 61.7, 62.4, 81.4, 87.4, 107.6, 118.2, 122.6, 132.3, 133.5, 141.1, 153.1, 153.7; GC-MS R_t = 21.743 min, *m/z* 88 (13), 114 (24), 115 (28), 117 (22), 143 (100), 144 (18), 170 (77), 171 (12), 215 (20); HRMS (+ES) calcd for $C_{14}H_{15}NO_4Na$ 284.0899, found 284.0911.

Ethyl 3-2-{[(*tert*-Butoxycarbonyl)amino]phenyl}prop-2-ynoate (31c):[12] obtained in 36% yield (76 mg, 0.40 mmol) as colorless pure oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, 3H, J = 7.1 Hz), 1.55 (s, 9H), 4.33 (q, 2H, J = 7.1 Hz), 7.00 (dt, 1H, J_d = 1.1 Hz, J_t = 7.6 Hz), 7.19 (s, 1H), 7.43 (t, 1H, J = 7.4 Hz), 7.51 (dd, 1H, J = 1.3, 7.8 Hz), 8.20 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 30.2, 64.3, 83.3, 89.3, 109.3, 120.1, 124.3, 134.2, 135.4, 143.5, 154.2, 155.7; GC-MS R_t = 22.286 min, *m/z* 57 (86), 59 (54), 88 (15), 89 (22), 114 (25), 115 (37), 117 (65), 143 (100), 144 (28), 170 (76), 189 (46); HRMS (+ES) *m/z* calcd for $C_{16}H_{19}NO_4Na$ 312.1212, found 312.1222.

■ ASSOCIATED CONTENT

Supporting Information. Figures giving NMR spectra (^{1}H NMR and ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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