JOC Article
pubs.acs.org/joc

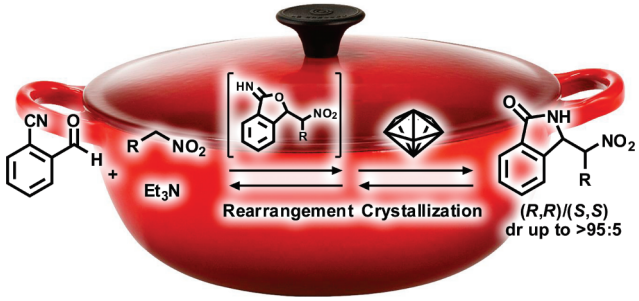
Diastereoselective One-Pot Tandem Synthesis of 3-Substituted Isoindolinones: A Mechanistic Investigation

Marcus Angelin, Martin Rahm, Andreas Fischer, Tore Brinck, and Olof Ramström*

KTH, Royal Institute of Technology, Department of Chemistry, Teknikringen 30, S-10044 Stockholm, Sweden

ramstrom@kth.se

Received May 14, 2010



The mechanism of a base-catalyzed one-pot reaction of 2-cyanobenzaldehyde and primary nitroalkanes, to produce 3-substituted isoindolinones, has been investigated. A route starting with a nitroaldol (Henry) reaction, followed by a subsequent cyclization and rearrangement, was supported by intermediate analogue synthesis and DFT calculations. Direct diastereoselective crystallization from the reaction mixture was also achieved and studied for a number of substrates. Furthermore, the 3-substituted isoindolinones are an interesting group of compounds, both present important natural products, as well as being precursors to other valuable building blocks.

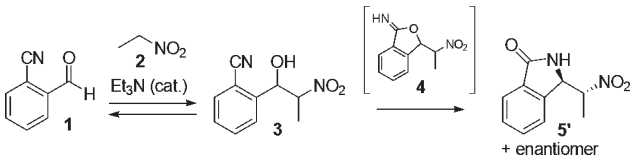
Introduction

3-Substituted isoindolinones form the core structure in a large amount of biologically active natural products and pharmaceutically interesting compounds.[1−10] They are also employed for other applications, such as serving as effective chiral auxiliaries.[11,12] Considering their wide range of applications and therapeutic potencies, the interest for 3-substituted isoindolinones has grown over the past decades. A large number of synthetic methods have been developed, and a few have also been able to generate products stereoselectively.[13−15] However, the methodologies are often complex and nonflexible, making the synthetic processes cumbersome. These facts open the field for new, simple, and effective routes toward these synthetically and biologically interesting motifs.

(1) Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett*. **1982**, *23*, 39–42.
(2) Valencia, E.; Fajardo, V.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett*. **1985**, *26*, 993–996.
(3) Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett*. **1984**, *25*, 599–602.
(4) Salvetti, A.; Ghiadoni, L. *J. Am. Soc. Nephrol*. **2006**, *17*, S25–S29.
(5) Stuk, T. L.; Assink, B. K.; Bates, R. C., Jr.; Erdman, D. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L. *Org. Process Res. Dev*. **2003**, *7*, 851–855.
(6) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1499–1502.
(7) Ferland, J. M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem*. **1985**, *63*, 361–365.
(8) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem*. **1994**, *59*, 2623–2625.
(9) Taylor, E. C.; Zhou, P.; Jennings, L. D.; Mao, Z.; Hu, B.; Jun, J.-G. *Tetrahedron Lett*. **1997**, *38*, 521–524.
(10) Zhuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, H. F. *J. Med. Chem*. **1998**, *41*, 157–166.
(11) McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69–79.
(12) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett*. **1990**, *31*, 5015–5018.
(13) Chen, M.-D.; He, M.-Z.; Zhou, X.; Huang, L.-Q.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2005**, *61*, 1335–1344.
(14) Deniau, E.; Couture, A.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2008**, *19*, 2735–2740.
(15) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2008**, *19*, 111–123.

Published on Web 08/06/2010 DOI: 10.1021/jo100868z

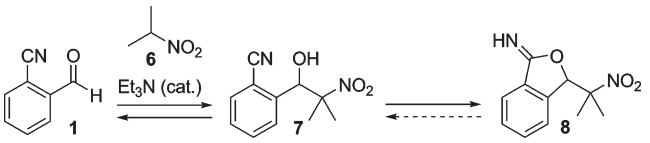
SCHEME 1. Synthesis of Isoindolinone 5′ in a Diastereoselective One-Pot Tandem Reaction−Crystallization Protocol



In some of our more recent work,[16,17] directed toward the field of dynamic combinatorial chemistry (DCC),[18−28] we demonstrated how a subsequent and irreversible tandem reaction could drive a dynamically interchanging system of nitroaldol adducts, forming the unexpected 3-nitroethylsubstituted isoindolinone **5**, hypothetically through an intermediate iminophthalan **4** (Scheme 1).[16] The product could also be produced stereoselectively through coupling with diastereomeric crystallization in a one-pot procedure.[17] From a synthetic viewpoint, this one-pot sequence of a tandem nitroaldol rearrangement reaction and subsequent crystallization is highly interesting. It represents a new convenient route to the isoindolinone core structure and also presents an opportunity for stereoselection. Moreover, the introduced nitro group could work as a handle for further derivatization and also makes the compounds into 1,2-diamine precursors. The 1,2-diamine motif is present in a wide range of compounds having a broad range of functions, reaching from important natural products and drugs to ligands in metal-mediated catalysis and organocatalysis.[29−33]

In order to develop this reaction system further, it is important to understand the reaction mechanism and the crystallization process. A few other tandem reactions using 2-cyanobenzaldehyde, or the analogue ester methyl 2-formylbenzoate, but employing other conditions and different nucleophiles, have been reported.[34−36] In these cases, a possible iminolactam-like intermediate is often mentioned in the mechanistic discussions. However, only in one case[34] is evidence for such a species provided. Aside from that, mechanistic suggestions have only been hypothesized. In this paper, we present a mechanistic study of our isoindolinone-forming tandem reaction. This is based on isolating an intermediate analogue, combined with density functional theory (DFT) calculations. We also investigate the coupled crystallization process which provides highly diastereoenriched 3-substituted isoindolinones in high yield and with no need of further purification.

SCHEME 2. Synthesis of Intermediate Analogue 8



Results and Discussion

Upon structural examination of the proposed intermediate iminophthalan **4**,[16] one can notice the presence of a rather acidic proton in the position α to the nitro group. This could be the key element for further progress of the reaction, and its removal could present an opportunity to trap the reaction at this stage. To this end, an analogous experiment was designed, reacting 2-cyanobenzaldehyde **1** with 2-nitropropane **6** in the presence of triethylamine. This experiment would, assuming a correct hypothesis, form the analogous iminophthalan **8**, carrying no acidic proton and thereby trapping it from further transformation to the isoindolinone. The reaction was performed in an NMR tube and followed continuously by ^{1}H NMR spectroscopy. After being left overnight, all starting material had been converted into a single product. Purification of this product proved to be very difficult. The reaction reversed on silica, and mostly starting material could be isolated. However, a small fraction of pure material could be collected and further characterized by ^{1}H/^{13}C NMR spectroscopy and HRMS. To provide further evidence, a single crystal of the final cyclized product was produced, and consequent X-ray diffraction analysis proved the compound to be iminophthalan **8** (Scheme 2).

After having isolated iminophthalan **8**, it seemed likely that the reaction under study would follow the same reaction path, in this case via intermediate **4**. A mechanistic route to this species would go through the confirmed nitroaldol reaction and then undergo triethylamine-assisted cyclization. This would form compound **4**, from nitroaldol adduct **3**, only passing through one transition state (Figure 1). The viability of this reaction step was confirmed by DFT calculations, where the effect of the solvent (acetonitrile) was implicitly considered using a continuum method. To allow for faster convergence of the transition state queries, the smaller base trimethylamine was used instead of triethylamine. Figure 1 shows how the cyclization proceeds in one step through **TS1**, with a free energy of activation of 24 kcal/mol. If the one-step cyclization and proton transfer reaction were to take place without the assisting base, the barrier would rise considerably and exceed 50 kcal/mol.

With the cyclization part of the mechanism established, the focus now shifted to the final rearrangement step. From the successful trapping of iminophthalan **8**, it had become

(16) Angelin, M.; Vongvilai, P.; Fischer, A.; Ramström, O. *Chem. Commun*. **2008**, 768–770.
(17) Angelin, M.; Fischer, A.; Ramström, O. *J. Org. Chem*. **2008**, *73*, 3593–3595.
(18) Cheeseman, J. D.; Corbett, A. D.; Gleason, J. L.; Kazlauskas, R. J. *Chem.—Eur. J*. **2005**, *11*, 1708–1716.
(19) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev*. **2006**, *106*, 3652–3711.
(20) Crego-Calama, M.; Reinhoudt, D. N.; ten Cate, M. G. J. *Top. Curr. Chem*. **2005**, *249*, 285–316.
(21) de Bruin, B.; Hauwert, P.; Reek, J. N. H. *Angew. Chem., Int. Ed*. **2006**, *45*, 2660–2663.
(22) Haussmann, P. C.; Stoddart, J. F. *Chem. Rec*. **2009**, *9*, 136–154.
(23) Huc, I.; Nguyen, R. *Comb. Chem. High Throughput Screening* **2001**, *4*, 53–74.
(24) Klekota, B.; Miller, B. L. *Trends Biotechnol*. **1999**, *17*, 205–209.
(25) Lehn, J.-M. *Chem. Soc. Rev*. **2007**, *36*, 151–160.
(26) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331–2332.
(27) Ramström, O.; Lehn, J.-M. *Nat. Rev. Drug Discovery* **2002**, *1*, 26–36.
(28) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed*. **2002**, *41*, 898–952.
(29) Bennani, Y. L.; Hanessian, S. *Chem. Rev*. **1997**, *97*, 3161–3195.
(30) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des*. **2006**, *67*, 101–114.
(31) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed*. **1998**, *37*, 2580–2627.
(32) Nakayama, K.; Maruoka, K. *J. Am. Chem. Soc*. **2008**, *130*, 17666–17667.
(33) Cardona, F.; Goti, A. *Nat. Chem*. **2009**, *1*, 269–275.
(34) Sato, R.; Ohmori, M.; Kaitani, F.; Kurosawa, A.; Senzaki, T.; Goto, T.; Saito, M. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 2481–2485.
(35) Sato, R.; Senzaki, T.; Goto, T.; Saito, M. *Chem. Lett*. **1984**, 1599–602.
(36) Song, Y. S.; Lee, C. H.; Lee, K.-j. *J. Heterocycl. Chem*. **2003**, *40*, 939–941.

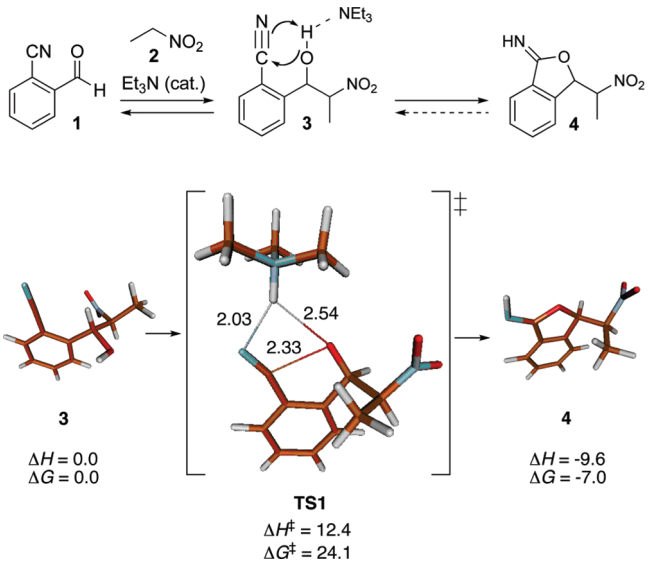


FIGURE 1. Proposed mechanism for the cyclization to form the intermediate iminophthalan **4**. The bottom part displays optimized geometries of β-nitroalcohol **3** and iminophthalan **4** in acetonitrile, and their interconnecting transition state **TS1**. Bond lengths are given in angstroms. Relative energies are calculated for 1 M concentration and 298 K at the B3LYP/6-31+G(d,p) level of theory in acetonitrile.

clear that the proton α to the nitro group was key to initiate the rearrangement. Having catalytic amounts of base present, the first step would be abstracting this proton, forming anion **9**. This species can then push the electrons through the molecule, opening up the ring system, in what would be a conjugate base type elimination. This results in the unstable intermediate **10**, which immediately would ring-close and form **11** in a practically irreversible 1,4-addition to the nitrostyrene moiety. Final protonation, by the triethylammonium salt, would result in the final rearranged isoindolinone **5**. Again, DFT calculations were used to investigate the viability of the proposed mechanism (Figure 2). The energies, which are given relative to compound **3** and free trimethylamine, show that the overall rate-determining step is the cyclization in **TS1**, in agreement with the experiments.[16] The proton abstraction in **TS2** is the second largest energy barrier, while the subsequent reaction steps through **TS3** and **TS4** proceed rapidly. The reported relative enthalpy of **TS3** appears lower than for intermediate **10**; however, this is a computational artifact that originates from the gas-phase enthalpy correction. The final protonation step (**11** → **5**) was not investigated in more detail but is also likely to proceed at a rapid rate (Figure 2).

Having acquired evidence supporting the mechanistic pathway, efforts were now put into investigating the crystallization process. In earlier work by our group, isoindolinone **5′** has been isolated in high yield and good diastereomeric ratio.[17] The best results were obtained when performing the reaction in a mixture of chloroform and hexane. It was also observed that the other diastereomer **5″** was thermodynamically favored and present in excess in solution. The reason for diastereomer **5′** being the preferred structure in the formed precipitation could be due to one or a combination of several factors. Reaction kinetics could be involved: if compound **5′** would form at a higher rate and reach the limit of solubility before establishing the diastereomeric equilibrium, precipitation would take place, thereby excluding the possibility for conversion to the opposite isomer. Solubility differences of the diastereomers due to different supramolecular interactions in solution could also be involved. This would result in faster supersaturation of compound **5′**, initiating the crystallization process. Consequently, compound **5′** would be largely excluded from the solution equilibrium. The equilibrium would then be reinstated by proton abstraction by triethylamine, forming more **5′**, which then would continue to precipitate until all material has been consumed.

Initially, the reaction kinetics for the respective diastereomers of **5** was studied by performing the reaction in deuterated chloroform. It could clearly be seen that compound **5′** was the kinetically favored isomer, initially formed at a considerably higher rate, to subsequently succumb to the thermodynamic pressure from the other diastereomer (see Supporting Information). This observation suggests that the reaction kinetics plays a substantial role in the crystallization process. It is also coherent with certain observations at optimized reaction conditions. In this case, precipitation starts relatively quickly, in a time frame where the kinetic product definitely would be dominating in solution.

If the reaction kinetics is indeed an important factor for the crystallization-driven step, the diastereomeric ratio in the precipitate should be affected by the reaction concentration. At high concentrations, the precipitation threshold would be reached relatively fast, allowing less time for the competing proton abstraction process to occur. At lower concentrations, however, there will be more time for the thermodynamic product to compete, resulting in lower diastereomeric ratios. In order to challenge this hypothesis, reactions were carried out at three different concentrations (0.125, 0.094, and 0.063 M in 1:1 chloroform/hexane), and the formed precipitates were analyzed by ^{1}H NMR spectroscopy. The results supported the model, and an increase in diastereomeric ratio was obtained when performed at higher concentrations. The increase, however, did not follow a linear correlation to the concentration, and a much larger increase was seen when moving from the lowest concentration. This could be due to the location of the threshold limit between these two concentrations (for spectra, see Supporting Information).

There is a possibility that supramolecular interactions in the solution, or properties of the actual crystallization process, could provide complementary explanations for the observed diastereoenrichment. If reaction kinetics would be the only factor inducing precipitation from a reaction mixture, which already has gone to completion without precipitating, this should give a diastereomeric ratio in the crystals similar to the thermodynamic composition in the solution. To investigate this, a reaction was prepared in solely deuterated chloroform (0.125 M) to avoid precipitation. The reaction was monitored, and when it had reached completion, an equal volume of hexane was added to induce precipitation. The isolated precipitate still showed an enrichment of diastereomer **5′**, indicating that factors other than kinetics, such as supramolecular solution interactions, are also involved. Another factor that could support this phenomenon is the observed peak shifting in the ^{1}H NMR spectrum when larger amounts of compound **5** have been formed (see Supporting Information).

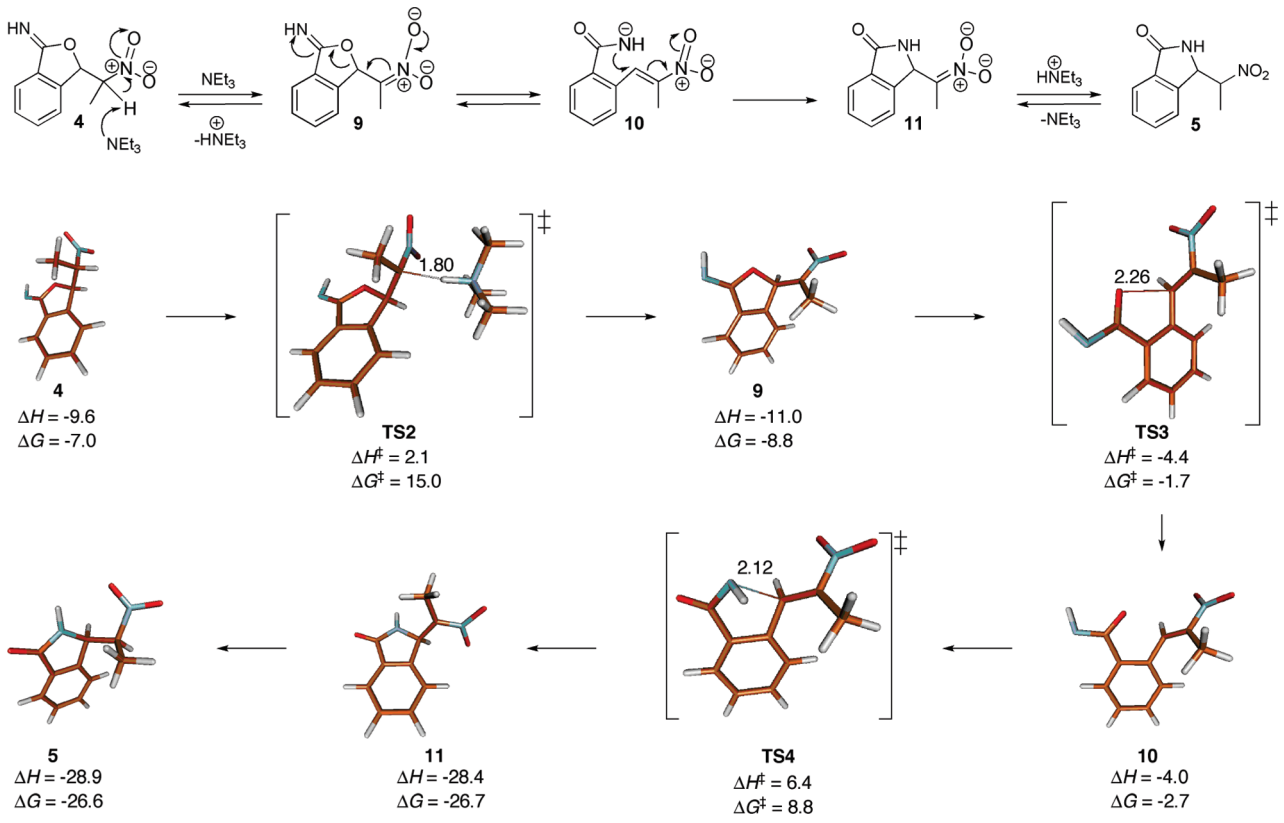
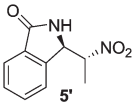
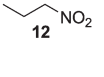
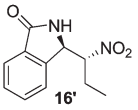
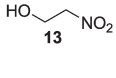
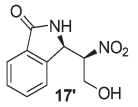
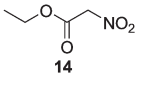
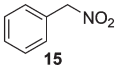


FIGURE 2. Proposed rearrangement mechanism to form isoindolinone **5** from intermediate iminophthalan **4**. The bottom part displays optimized intermediate structures and their interconnecting transition states. Enthalpies and Gibbs free energies are shown relative to compound **3** in Figure 3. Bond lengths are given in angstroms. Relative energies are calculated for 1 M concentration and 298 K at the B3LYP/6-31+G(d,p) level of theory in acetonitrile.

In order to possibly find out more about the interaction phenomenon, and to investigate its generality, it was of interest to screen a few other substrates. To this end, nitroalkanes **12**−**15** were tested in the reaction with 2-cyanobenzaldehyde **1**. The results are summarized in Table 1.

Nitroethane was used in order to reproduce the results from our earlier study.[17] This worked well, and compound **5** could be isolated in pure form, with a large diastereomeric preference for diastereomer **5′**, after simple filtration (entry 1). Using these optimized reaction conditions (0.25 M **1**, 0.275 M nitroalkane, 0.1 M Et_3N in 1:1 $CHCl_3$/hexane), the reaction was applied to nitroalkanes **12**−**15**. Unfortunately, these conditions did not work well in the other cases. However, after addressing each reaction condition individually, effective procedures could be found for several of the substrates (entries 2 and 3). Nitropropane **12** did work with the initial reaction conditions. However, the formed precipitate was of microcrystalline character, and the extra small pore filter papers, which were used in the case of nitroethane **5**, still allowed particles to pass through, thereby reducing the yield. To solve this problem, the reaction was performed in a capped syringe and filtered through a glass fiber filter after completion (see Supporting Information for experimental setup). With this procedure, compound **16** could be isolated in good yield and diastereomeric ratio (entry 2). When using nitroalkanol **13** (entry 3), the solvent system had to be changed in order to obtain a precipitation. In a mixture of ethyl acetate and hexane, product **17** was possible to isolate in reasonable yield and dr. Fortunately, the diastereomeric ratio could in this case be greatly improved by a single recrystallization.

TABLE 1. Diastereoselective One-Pot Synthesis of Various 3-Substituted Isoindolinones

Entry	Nitroalkane	Product	Yield[a]	dr[b]
1	 **2**	 **5′**	84	94:6
2	 **12**	 **16′**	90	90:10
3	 **13**	 **17′**	72	83:17[c]
4	 **14**	-	-	-
5	 **15**	-	-	-

[a]Isolated yield. Due to the microcrystalline properties of the precipitations, some material was lost during the filtration step, thereby limiting the yield. [b](*R*,*R*),(*S*,*S*):(*R*,*S*)/(*S*,*R*). [c]Diastereomeric ratio was improved to >95:5 after a single recrystallization from EtOH.

Less successful was the procedure when using ethyl 2-nitroacetate **14** and (nitromethyl)benzene **15** (entries 4 and 5). In the former case, a mixture of several products was formed in the

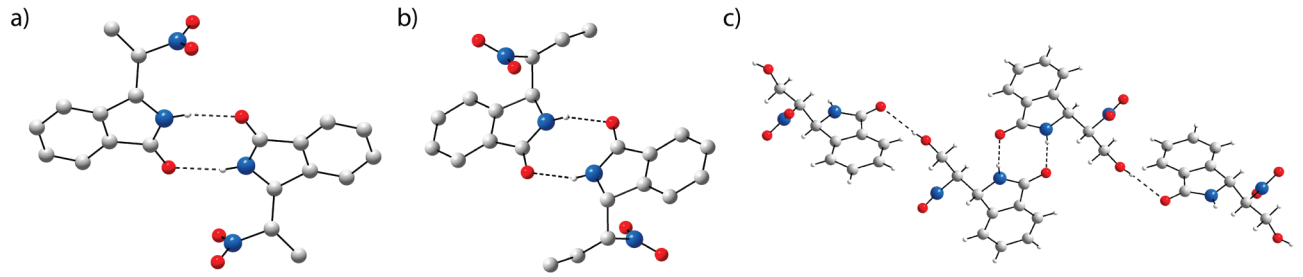


FIGURE 3. Crystal structures of isoindolinones **5′**, **16′**, and **17′**. (a) Crystal packing of **5′** in centrosymmetric dimers; (b) crystal packing of **16′** in centrosymmetric dimers; (c) crystal packing of **17′** in centrosymmetric chains.

reaction and no precipitation occurred. In the latter, the reaction proved sluggish, probably due to steric demand, and the only observed conversion was to unknown products, probably resulting from decomposition of the rather unstable (nitromethyl)benzene **15**.

Finally, single-crystal X-ray crystallographic data were obtained and compared between the isoindolinone products (Figure 3). All three structures crystallize in centrosymmetric space groups, are racemic, and possess (*R*,*R*)/(*S*,*S*)-configuration. Isoindolinone **16′** crystallized in a much similar fashion to structure **5′**,[16,17] forming centrosymmetric dimers in the crystalline state, held together by hydrogen bonding (Figure 3a,b). Product **17′**, however, expectedly displayed different crystal packing, stemming from the presence of an additional H-bond donor. This leads to further H-bonding between molecules, yielding infinite chains (Figure 3c).

Conclusions

The mechanism of the formation of 3-substituted isoindolinones from 2-cyanobenzaldehyde **1** and primary nitroalkanes has been investigated. By using secondary nitroalkane **6**, the most acidic proton was eliminated from the molecule and the reaction could be halted at intermediate iminophthalan **8**, which was isolated and characterized by X-ray crystallography. This strongly suggested a mechanism proceeding through a nitroaldol reaction, followed by a cyclization and a rearrangement to produce the final isoindolinone. Further evidence supporting this mechanistic hypothesis was provided using DFT calculations, and these results were in agreement with reported kinetic studies.[16] The diastereoselective crystallization phenomenon, which is present during these reactions, was also investigated, and the selectivity seems to arise from a combination of kinetic factors in the formation of each diastereomer and stacking effects in solution which affected the solubility of the diastereomers. Although the precise stacking interactions were not studied, indications were given through X-ray crystallographic analysis on isoindolinone **5′**, as well as the other synthesized isoindolinones **16′** and **17′**.

Experimental Section

General Methods. All commercially available starting materials and solvents were of reagent grade and used as received. ^{1}H and ^{13}C spectra were recorded at 400 (100) MHz and/or 500 (125) MHz, respectively. Spectra were recorded at 298 K in $CDCl_3$ (residual peaks ^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.16), DMSO (residual peaks: ^{1}H: δ = 2.50 ppm; ^{13}C: δ = 39.52), or MeOD (residual peaks: ^{1}H: δ = 3.31 ppm; ^{13}C: δ = 49.00) and were calibrated after the solvent residual peaks.

Computational Methods. All stationary points and transition states were first optimized at the B3LYP/6-31+G(d,p) level in gas phase using Gaussian 03.[37] Thermodynamic corrections were obtained using analytical force constants at the same level of theory. Solution energies in acetonitrile were obtained after reoptimization of all geometries, using the default solvation method implemented in the Jaguar[38] code. Due to only minor structural differences of the species in gas phase and in solution, the thermodynamic corrections obtained from the gas-phase frequencies have been used with the final solution energies.

(Nitromethyl)benzene (15):[39] Yellow liquid (1.1 g, 85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (br s, 2H), 7.32−7.44 (m, 5H).

3-(1-Nitroethyl)isoindolin-1-one (5):[16,17] White powder (87 mg, 84%, dr (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 94:6); ^{1}H NMR (500 MHz, DMSO) δ 1.56 (d, J=6.8 Hz, 3H), 5.11 (d, J=3.3 Hz, 1H), 5.33 (dq, J=3.3 Hz, J=6.8 Hz, 1H), 7.49−7.56 (m, 1H), 7.61−7.67 (m, 3H), 9.03 (s, 1H); mp 177−179 °C.

3-(1-Nitropropyl)isoindolin-1-one (16). The reaction was performed in a capped syringe, equipped with a Chromafil GF-100/15 glass fiber filter (pore size = 1.0 μL) (page S5 in Supporting Information). Triethylamine (20.2 mg, 27.9 μL, 0.2 mmol) was added to a solution of 2-cyanobenzaldehyde **1** (65.6 mg, 0.5 mmol) and 1-nitropropane **12** (49.0 mg, 49.1 μL, 0.55 mmol) in chloroform (1 mL). Hexane (1 mL) was slowly added to the solution, which then was stirred overnight. The formed precipitate was filtered by pressing the supernatant through the filter-equipped syringe. It was washed with cold toluene, affording pure isoindolinone **16** as a fine white powder (99 mg, 90%, dr (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 90:10). The reaction could also be performed in the same fashion as **5**. This, however, resulted in lower yield due to material loss during the filtration: ^{1}H NMR (500 MHz, MeOD) δ 1.04 (t, J = 7.4 Hz, 3H), 1.95−2.08 (m, 1H), 2.14−2.27 (m, 1H), 4.99 (dt, J = 4.1 Hz, J = 10.4 Hz 1H), 5.13 (d, J = 4.1 Hz, 1H), 7.53−7.71 (m, 1H), 7.64−7.70 (m, 2H), 7.76 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, MeOD) δ 10.7, 24.9, 59.5, 91.4, 124.5, 125.1, 130.3, 133.4, 144.1, 172.8; mp 140−142 °C; HRMS (FAB+) calcd for $C_{11}H_{13}N_2O_3$ $[M + H]^+$ m/z = 221.0928, found 221.0927.

(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03*; Gaussian Inc.: Wallingford, CT, 2004.
(38) *Jaguar 6.0*, Schrödinger, LLC: Portland, OR, 2005.
(39) Baruah, A.; Kalita, B.; Barua, N. C. *Synlett* **2000**, 1064–1066.

3-(2-Hydroxy-1-nitroethyl)isoindolin-1-one (17). Triethylamine (20.2 mg, 27.9 μL, 0.2 mmol) was added to a solution of 2-cyanobenzaldehyde **1** (65.6 mg, 0.5 mmol) and 2-nitroethanol **13** (50.1 mg, 39.4 μL, 0.55 mmol) in ethyl acetate (1 mL). Hexane (600 μL) was added slowly, in 200 μL fractions, and the mixture was stirred overnight. The formed precipitate was filtered and washed with cold toluene, affording the pure isoindolinone **17** as a lightly colored powder (80 mg, 72%, dr (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 83:17). A single recrystallization from ethanol improved the diastereomeric ratio to >95:5: ^{1}H NMR (500 MHz, DMSO) δ 3.80 (ddd, J = 3.4, 4.7, 15.5 Hz, 1H), 4.02 (ddd, J = 6.2, 9.1, 15.5 Hz, 1H), 4.93 (ddd, J = 3.4, 5.7, 9.1 Hz, 1H), 5.15 (d, J = 5.7 Hz, 1H), 5.44 (dd, J = 4.7, 6.2 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 54.9, 60.0, 91.2, 123.2, 123.5, 129.1, 132.1, 132.2, 142.5, 169.2; mp 166−167 °C; HRMS (FAB+) calcd for $C_{10}H_{11}N_2O_4$ $[M + H]^+$ m/z = 223.0725, found 223.0722.

Isolation of Intermediate Analogue, Iminophthalan (8). 2-Cyanobenzaldehyde **1** (32.8 mg, 0.25 mmol) and 2-nitropropane **6** (24.5 mg, 24.7 μL, 0.275 mmol) were dissolved in deuterated chloroform (0.5 mL). Triethylamine (10.1 mg, 13.9 μL, 0.1 mmol) was added, and the mixture was followed by ^{1}H NMR until all aldehyde had been consumed into a single product. For identification purposes, the mixture was evaporated and subjected to flash chromatography (CH_2Cl_2/hexane). Although most of the product reversed back to starting material during chromatography, a small amount was isolated and analyzed by NMR spectroscopy and HRMS. It was also possible to obtain a single crystal which with certainty could identify the product to be 3-(2-nitropropan-2-yl)isobenzofuran-1(3*H*)-imine **8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.57 (s, 3H), 5.97 (s, 1H), 7.22−7.26 (m, 1H), 7.49.7.56 (m, 2H), 7.83−7.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 22.5, 84.8, 89.6, 122.6, 124.4, 130.1, 132.7, 141.9, 166.6; HRMS (ESI+) calcd for $C_{11}H_{13}N_2O_3$ $[M]^+$ m/z = 221.0926, found 221.0922.

Kinetic Study of the Formation of Isoindolinone Diastereomers 5′ and 5″ in Solution. 2-Cyanobenzaldehyde (6.56 mg, 0.125 mmol) and nitroethane (0.1375 mmol) were dissolved in deuterated chloroform (1 mL). Triethylamine (5.06 mg, 6.97 μL, 0.05 mmol) was added, and the reaction composition was followed by ^{1}H NMR spectroscopy. No precipitation occurred.

Study of the Precipitation Composition of Isoindolinone 5 at Different Concentrations. Three experiments were compared (a, b, c). Triethylamine (a, 0.1 mmol; b, 0.075 mmol; c, 0.05 mmol) was added to a solution of 2-cyanobenzaldehyde **1** (a, 0.5 mmol; b, 0.25 mmol; c, 0.125 mmol) and nitroethane **2** (a, 0.55 mmol; b, 0.275 mmol; c, 0.1375 mmol) in chloroform (1 mL). Hexane (1 mL) was slowly added to the solutions, which then were stirred and until around 24 h after first sign of precipitation. The precipitates were filtered, and the diastereomeric compositions were analyzed by ^{1}H NMR: dr (a) (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 92:8; (b) (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 87:13; (c) (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 66:38. For comparison, normal synthesis of **5** is performed at twice the concentration of (a).

Precipitation of Isoindolinone 5 from a Thermodynamically Controlled Reaction Process. Triethylamine (5.1 mg, 7.0 μL, 0.05 mmol) was added to a solution of 2-cyanobenzaldehyde **1** (16.4 mg, 0.125 mmol) and nitroethane **2** (10.3 mg, 9.9 μL, 0.1375 mmol) in deuterated chloroform (1 mL). The mixture was stirred at room temperature and followed by ^{1}H NMR until the reaction was almost complete and under thermodynamic control (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 25:75. Hexane (1 mL) was added, which induced a precipitation after some time. The mixture was left overnight, whereafter the precipitate was filtered and analyzed: dr (*R*,*R*)/(*S*,*S*):(*R*,*S*)/(*S*,*R*) = 73:27.

Acknowledgment. This study was supported by the Swedish Research Council, and M.A. gratefully acknowledges financial support from the Royal Institute of Technology's Excellence Award.

Supporting Information Available: Additional figures, ^{1}H/^{13}C NMR spectra, computational data and crystallographic (CIF) files are available. This material is available free of charge via the Internet at http://pubs.acs.org.