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Synthesis of 2*H*-pyrroles via the 1,3-dipolar cycloaddition reaction of nitrile ylides with acrylamides

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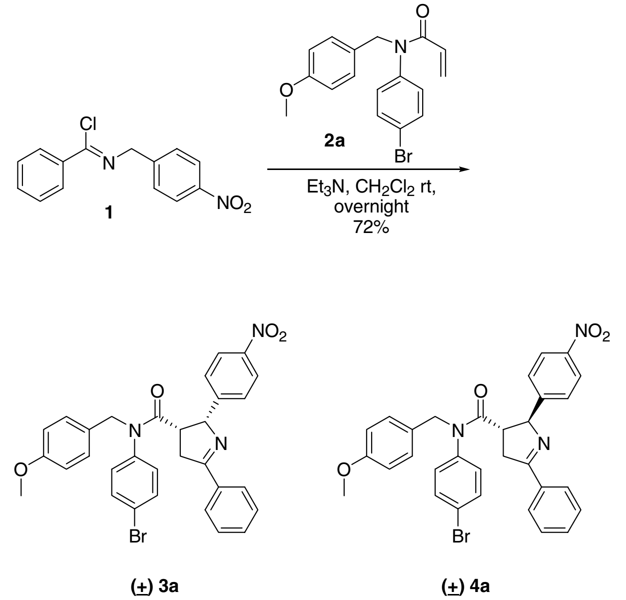
Abstract—3,4-Dihydro-2*H*-pyrrole derivatives were synthesized by the 1,3-dipolar cycloaddition reaction of nitrile ylides with acrylamides. Acrylamide substitution patterns and benzimidoyl chloride equilibration were investigated.

In 1962, Huisgen reported the first nitrile ylide example—the product of treating *N*-(4-nitrobenzyl)benzimidoyl chloride (**1**) with triethyl amine at 0–20 °C.[1] The resulting nitrile ylide was reacted with dipolarophiles such as acrylonitrile, methyl acrylate, and acrylic acid to generate pyrrole derivatives in good yields. Over the ensuing 40+ years, the 1,3-dipolar cycloaddition reactions of nitrile ylides with a variety dipolarophiles have been studied by many research groups.[2–12] Since the cycloaddition reactions of 1,3-dipoles and their application in solid phase synthesis are central to our research interests,[13–18] we were naturally interested in applying nitrile ylide chemistry in our work. In reviewing the nitrile ylide literature, we were surprised to learn that no nitrile ylide–acrylamide cycloadditions had been reported and this observation became the starting point for the study reported here.

Our work began with *N*-(4-nitrobenzyl)benzimidoyl chloride **1** and *N*-(4-bromophenyl)-*N*-(4-methoxybenzyl)-acrylamide (**2a**) (Scheme 1).[19] We selected **1** for both historical—it was Huisgen's choice for his pioneering work—and practical—**1** is readily prepared from *N*-(4-nitro-benzyl)-benzamide and thionyl chloride—reasons. Acrylamide **2a** was selected because of our interest in eventually applying this chemistry to solid phase synthesis; that is, the 4-methoxybenzyl moiety in **2a** mimics a resin linker which would be cleavable at the end of the solid phase synthesis and the *p*-bromophenyl moiety would allow for coupling-based introduction of diversity. In the event, treating **1** with Et_3N and **2a** at ambient temperature delivered the cis and trans diastereomers **3a** and **4a** in 72% yield in a 60:40 diastereomer ratio (Table 1, entry 1). As was the case in Huisgen's study of **1**+methyl acrylate,[20] we saw no evidence for the formation of regioisomers (Scheme 1). Cis and trans diastereomer assignments were initially established by analyzing the coupling constants for the benzylic methine proton in these 3,4-dihydro-2*H*-pyrroles wherein *cis*-**3a** was



Scheme 1. Synthesis of **3a** and **4a**.

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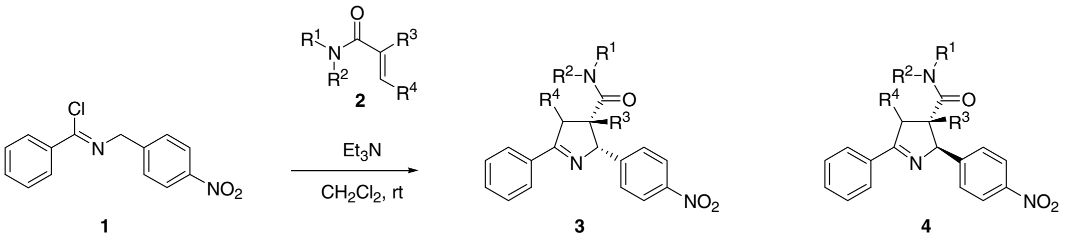
Table 1. Synthesis of 3,4-dihydro-2*H*-pyrroles by reaction of **1**+**2**+Et_3N



Entry	Acrylamide	R^1	R^2	R^3	R^4	Yield (%)[a]	Ratio of **3**/**4**
1	**2a**	4-$CH_3OC_6H_4CH_2$	4-BrC_6H_4	H	H	72[d]	60/40[c] (65/35)[b]
2	**2b**	CH_3	CH_3	H	H	73[d]	58/42[c] (60/40)[b]
3	**2c**	CH_3	CH_3	CH_3	H	0[e]	0
4	**2d**	CH_3	H	CH_3	H	10[e]	Trans[c]
5	**2e**	CH_3	CH_3	H	CH_3	Trace[e]	
6	**2f**	H	H	H	H	38[e]	Trans[c]
7	**2g**	H	H	CH_3	H	45[e]	21:79[c]

[a] Combined isolated yield.

[b] Isolated ratio of diastereomers.

[c] Ratio of diastereoisomers determined by 400 MHz ^1H NMR on crude mixtures.

[d] Reaction ran for overnight.

[e] Reaction ran for 3 days.

expected on the basis of dihedral angle considerations to have a larger coupling constant than *trans*-**4a**. For example, the literature values in related systems reveal a 9 Hz coupling constant for the cis isomer and a 6 Hz coupling constant for the trans isomer.[20] In our case, *cis*-**3a** has an 8.4 Hz coupling constant and *trans*-**4a** has a 7.2 Hz coupling constant. Given the narrowness of this difference in our system, we were pleased that these cis and trans assignments could be validated by X-ray crystallographic analysis of *cis*-**3a** (Fig. 1). Furthermore, *cis*-**3a** could be converted to *trans*-**4a** by treating isolated *cis*-**3a** with Et_3N in benzene under reflux for 18 h (Scheme 2). The cis:trans ratio of diastereomers formed in the reaction of **1** with methyl acrylate is 70:30 indicating[20] that methyl acrylate is slightly more cis-selective than acrylamide **2a**.

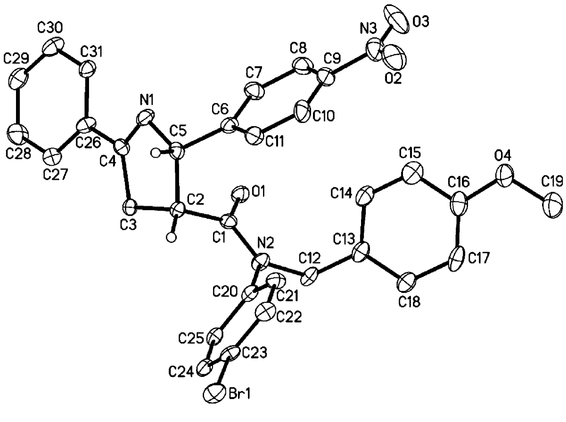
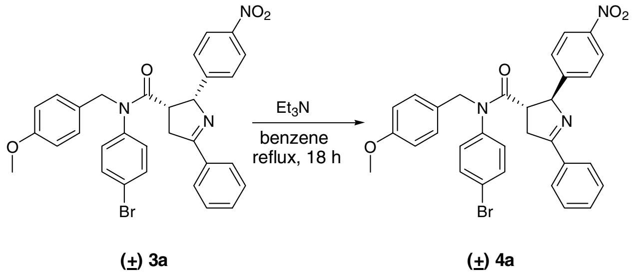


Figure 1. X-ray based ORTEP diagram of **3a**.



Scheme 2. Epimerization of *cis*-**3a** to *trans*-**4a**.

With these results in hand, we set out to explore how substituents R^1–R^4 in acrylamides **2** would affect the outcome of 1,3-dipolar cycloadditions with the nitrile ylide derived from **1**. The results are outlined in Table 1 with the reported diastereomer ratios having been determined by ^1H NMR analysis of the crude reaction mixture and the cis–trans stereochemical assignments established by NOE experiments.

The reaction of **1** with **2b** (entry 2) gave **3b** and **4b** in a 58:42 ratio, respectively, while the reaction of **1** with **2c** (entry 3) gave no product. Indeed, work-up of this latter reaction gave only *N*-(4-nitrobenzyl)-benzamide (i.e., hydrolysis of the nitrile ylide) and **2c**. The change from $R^3 = H$ (**2b**) to $R^3 = Me$ (**2c**) slightly perturbs the energy of the dipolarophile LUMO, increases the steric bulk of the dipolarophile, and, more importantly, causes the enone substructure to twist out of conjugation in order to avoid unfavorable steric interactions (Fig. 2; note that for **2c** only one conformer could be located).[21–23] A similar distortion is expected for the cycloaddition transition states.[22]

We next probed the consequence of removing a methyl substituent from nitrogen (i.e., **2d**) in order to avoid such distortions from planarity (although the slight electronic deactivation by the vinyl methyl group remains). This reaction (entry 4) gave **4d** in 10% yield and the crude NMR indicated only trace amounts of **3d**. We believe that epimerization of **3d** during the longer

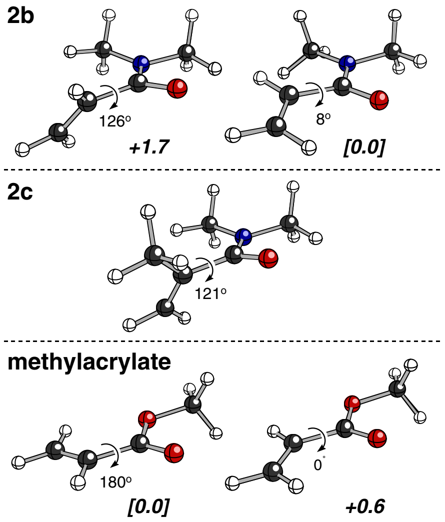


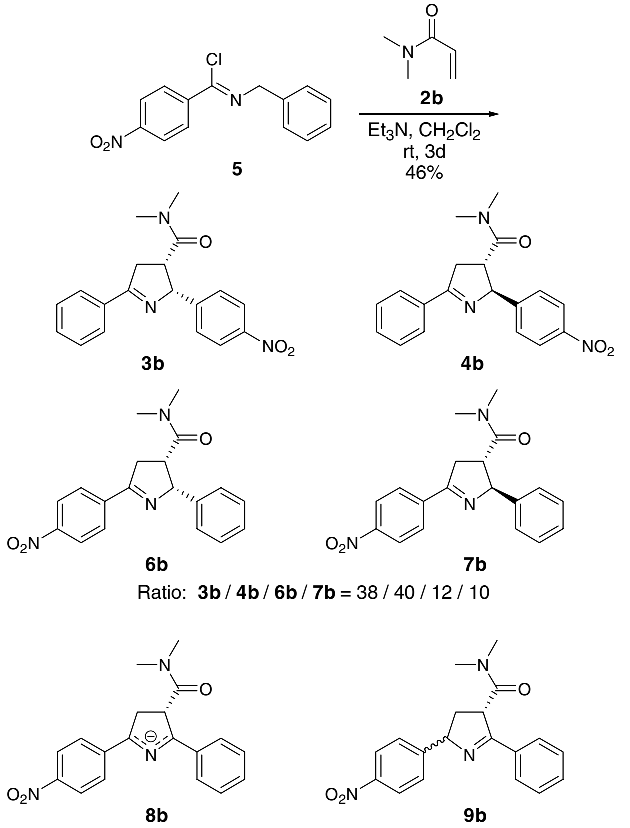
Figure 2. Preferred conformations of **2b**, **2c**, and methylacrylate (computed at the B3LYP/6-311 + G(d,p) level;[21–23] relative energies for pairs of conformers are shown in bold italics in kcal/mol).

reaction time (3 d) explains the apparent reversal in stereoselectivity. The 1,2-disubstituted alkene analog (**2e**; entry 5) gave only trace amounts of product—a result which parallels the reactivity of methyl crotonate versus methyl acrylate.[22]

The reaction of **1** with **2f** gave **4f** in 38% yield (entry 6) and the reaction of **1** with **2g** gave **3g** and **4g** in 45% yield (21:79 mixture of diastereomers, respectively; entry 7). This apparent reversal in diastereoselectivity is again believed to be related to the long reaction time and subsequent epimerization. The coupling constant for the distinctive benzylic proton in **4f** was 6.8 Hz.

With these 1,3-dipolar cycloaddition results for **1**+**2** in hand, we switched to a study of the reaction of **5** with acrylamide **2b** (Scheme 3). It has been reported and we have independently verified that the 1,3-dipolar cycloaddition reaction of **5** with methyl acrylate produces none of the product from nitrile ylide **5a** but instead produces only the product expected from **1a**, which was ascribed to the tendency of *N*-(benzyl)-4-nitrobenzimidoyl chloride (**5**) to rapidly rearrange to *N*-(4-nitrobenzyl)-benzimidoyl chloride (**1**) (Fig. 3).[20]

In contrast, we find that the reaction of **5** with **2b** leads to the formation of four products: **3b**+**4b** from nitrile ylide **1a** and **6b**+**7b** from nitrile ylide **5a** (Scheme 3). While attempts to separate these four products were unsuccessful, column chromatography did afford **3b**/**6b** and **4b**/**7b** mixtures (78:22 ratio; **3b**:**4b**:**6b**:**7b**::38:40:12:10). The different outcomes of reacting **5** with Et$_3$N and methyl acrylate[20] or *N*,*N*-dimethylacrylamide are still consistent with a rapid isomerization of **5** to **1**. This is a classic Curtin–Hammett situation in which unusually fast **2b**+**5a** reactions or unusually slow **2b**+**1a** reactions could shift the product ratio toward products resulting from **5a**. Note that at 25 °C, a difference in the energies of competing transition states of 0.8 kcal/mol corresponds to a product ratio of $\sim$4:1 (as for the reactions with **2b**) while an energy difference of 3 kcal/mol corresponds to a product ratio of $>$99:1 (as for the reactions with methylacrylate), suggesting that relatively subtle perturbations to the structures of the transition states for these reactions can lead to the observed results. More involved studies will be required to pin down these subtleties. We also note that in a study of the reaction of **5** with buckminsterfullerene [60],[25] Ovcharenko et al. reported constitutional isomers which appear to arise from reaction with both **1a** and **5a**.



Scheme 3. Reaction of imoyl chloride **5** with **2b**.

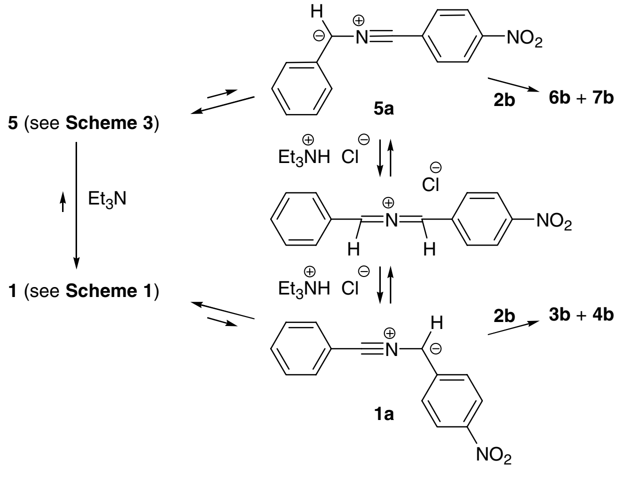


Figure 3. Equilibrium of benzimidoyl chloride **5** in the presence of Et$_3$N.[20,24]

Warming of the **3b**/**6b** mixture in the presence of Et$_3$N in benzene produces some unexpected results. As with the equilibration of *cis*-**3a** to *trans*-**4a** (Scheme 2), *cis*-**3b** converts to *trans*-**4b** under these conditions, but *cis*-**6b** and *trans*-**7b** do not equilibrate [note: the anions derived from *cis*-**3a** and *cis*-**3b** only protonate to give the imine out of conjugation with the nitrophenyl; a similar protonation of the anion derived from *cis*-**6b** (e.g., **8b**) might be expected to give *cis*/*trans*-**9b** instead of **7b**]. That *cis*-**6b** does not epimerize or rearrange to **9b** is surprising since, although the pK_a of toluene is more than 20 units higher than that of *p*-NO$_2$-toluene (43 vs 20 in DMSO),[26] deprotonation of either **3b** or **6b** should lead to very similar highly delocalized anions such as **8b**.[27] Quantum chemical calculations on models of **3b**/**4b**/**6b**/**7b** with no amide present also indicate that the imine prefers to be next to the phenyl group rather than the *p*-NO$_2$-phenyl group by 1–2 kcal/mol.[21] This dilemma could be resolved if **6b** actually exists instead as the enamine tautomer or as an adduct with adventitious water (or chloride; in these cases, the inherent acidity difference for protons next to phenyl and *p*-NO$_2$-phenyl groups could be manifested since delocalized anion **8b** would not be formed upon deprotonation), but these are ruled out by our spectroscopic data. Since carbonyl derivatives with *p*-NO$_2$-phenyl groups are significantly more electrophilic than those with phenyl groups,[28] we conjecture that rapid but reversible in situ addition to the imine group of **6b**—rather than deprotonation—predominates, thwarting its epimerization.

In summary, 1,3-dipolar cycloaddition reactions of benzonitrile(4-nitrobenzylide) (**1a**) and 4-nitrobenzonitrile-(benzylide) (**5a**) with acrylamides (**2a**–**g**) were successfully applied to the synthesis of 3,4-dihydro-2*H*-pyrrole derivatives (**3**, **4**, **6**, and **7**) with moderate to good yields.

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 290931. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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19. General procedure for the preparation of 3,4-dihydro-2*H*-pyrrole derivatives **3a** and **4a**: *N*-(4-nitro-benzyl)-benzimidoyl chloride **1** (0.413 g, 1.5 mmol) and *N*-(4-bromo-phenyl)-*N*-(4-methoxy-benzyl)-acrylamide **2a** (0.346 g, 1 mmol) in CH$_2$Cl$_2$ was treated with triethylamine (0.162 g, 1.6 mmol) under nitrogen atmosphere and stirred at room temperature for overnight. The reaction mixture was diluted with CH$_2$Cl$_2$ and washed with brine and water. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and the residue was purified by column chromatography (30% EtOAc in *n*-hexane) to give **3a** (273 mg, 47%) as yellowish solid and **4a** (147 mg, 25%) as yellowish wax. Compound **3a** was recrystallized from CHCl$_3$. Compound **3a**: mp 150–151 °C; IR(neat) 1641, 1626, 1613, 1596, 1513, 1341 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.13 (d, $J = 8$ Hz, 2H), 7.88 (d, $J = 7$ Hz, 2H), 7.53–7.35 (m, 7H), 6.70 (d, $J = 7$ Hz, 2H), 6.59 (s, 4H), 5.24 (d, $J = 8.4$ Hz, 2H), 4.89 (d, $J = 14$ Hz, 1H), 3.96 (d, $J = 14$ Hz, 1H), 3.77–3.62 (m, 2H), 3.72 (s, 3H), 3.15 (dd, $J = 16.8$ Hz and $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 174.4, 170.7, 159.2, 147.6, 146.9, 141.1, 133.6, 133.3, 131.5, 130.6, 130.5, 129.6, 128.9, 128.7, 128.3, 123.4, 122.7,113.7, 78.3, 55.4, 52.6, 45.3, 40.9; Compound **4a**: IR(neat) 1651, 1611, 1601, 1510, 1342 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.11 (d, $J = 8$ Hz, 2H), 7.80 (d, $J = 7$ Hz, 2H), 7.43–7.25 (m, 7H), 7.07 (d, $J = 8.4$ Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 2H), 6.43 (br s, 2H), 5.71 (d, $J = 7.6$ Hz, 1H), 4.86 (d,

$J = 14$ Hz, 1H), 4.75 (d, $J = 14$ Hz, 1H), 3.77 (s, 3H), 3.34 (m, 1H), 3.12 (m, 1H), 2.86 (q, $J = 8.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 159.5, 150.6, 147.4, 140.5, 133.5, 133.0, 131.5, 130.6, 130.2, 129.0, 128.8, 128.1, 127.6, 123.0, 122.6, 114.1, 79.2, 55.5, 52.0, 51.2, 42.2.

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