JOC*Article*

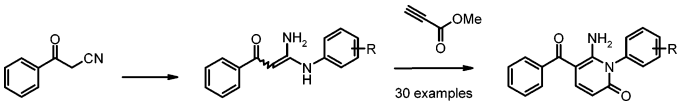
Efficient Regioselective Synthesis of 6-Amino-5-benzoyl-1-Substituted 2(1*H*)-Pyridinones

Hartmut Schirok,* Cristina Alonso-Alija, Jordi Benet-Buchholz,† Andreas H. Göller, Rolf Grosser, Martin Michels, and Holger Paulsen

Bayer HealthCare AG, Pharma Research, D-42096 Wuppertal, Germany

hartmut.schirok@bayerhealthcare.com

Received July 25, 2005



A regioselective and efficient approach toward 6-amino-5-benzoyl-1-substituted 2(1*H*)-pyridinones by reaction of acyclic ketene aminals with propiolic acid ester was developed. The effect of the solvent and temperature on the regioselectivity of the reaction and the compatibility of the target compounds to functional group manipulations was examined. Substrates with an ortho substituent build atropisomers due to the restricted rotation around the C−N bond. The enantiomers were separated, and the barrier of rotation was determined experimentally. Quantum chemical calculations allowed a ranking of the barrier heights, and a new mechanism of rotation by deformation of the central pyridinone moiety is proposed.

Introduction

Ketene aminals are powerful and versatile intermediates in heterocyclic synthesis. Reactions of cyclic ketene aminals of the general formula **1** with 1,2- and 1,3-bisacceptor substrates leading to five- and six-membered heterocycles have been reported repeatedly during the past three decades (Figure 1).[1] Depending on the electrophile used, a vast number of different heterocyclic structures is accessible. Among the six-membered ring systems, hydropyridines and pyridinones such as 2-aminotetrahydropyridines **2**,[2] 6-aminodihydropyridinones **3**,[3] 6-aminopyridinones **4**,[4] and dihydropyridine-2-amines **5**[5] have been synthesized, while the group of five-membered heterocycles includes aminopyrroles **6**,[6] 5-aminodihydropyrrolones **7-9**,[7] and 3-hydroxy-5-imino-1,5-dihydro-2*H*-pyrrol-2-ones **10**.[8] Furthermore, seven-membered 1*H*-imidazo[1,2-*b*][2]benzazepin-5-ones **11** are obtained with 2-(bromomethyl)benzoate.[9]

The two electron-donating amino groups on the one end and the electron-withdrawing effect of the carbonyl moiety on the other end of the ketene aminal system **1** cause a strong polarization of the remarkably long (1.38−1.47 Å) carbon−carbon double bond in the push−pull ethylene.[10] This determines the reactivity of the compound class **1**, which is characterized by the fact that the enaminic α-carbon atom is more nucleophilic than the two nitrogen atoms.[11] For example, simple electrophiles such as benzylic halides react selectively at the carbon atom (Figure 1, **1** → **12**).[7a,12]

* To whom correspondence should be addressed.
† Bayer Industry Services, Analytics, X-ray Laboratory, D-51368 Leverkusen, Germany. Present address: Institut Català d'Investigació Química (ICIQ), Avgda. Països Catalans, s/n, 43007 Tarragona, Spain.

(1) For reviews, see: (a) Huang, Z.; Wang, M. *Heterocycles* **1994**, *37*, 1233−1262. (b) Wang, M.; Huang, Z. *Prog. Natl. Sci.* **2002**, *12*, 249−257. For a more recent work, see: Sharon, A.; Maulik, P. R.; Roy, R.; Ram, V. J. *Tetrahedron Lett.* **2004**, *45*, 5815−5818.

(2) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Turner, I. *Tetrahedron* **1997**, *53*, 11781−11790.

(3) (a) Huang, Z.-T.; Liu, Z.-R. *Heterocycles* **1986**, *24*, 2247−2254. (b) Jones, R. C. F.; Smallridge, M. J. *Tetrahedron Lett.* **1988**, *29*, 5005−5008. (c) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Smallridge, M. J. *Tetrahedron* **1998**, *54*, 6191−6200.

(4) (a) Huang, Z.-T.; Tzai, L.-H. *Chem. Ber.* **1986**, *119*, 2208−2219. (b) Huang, Z.-T.; Liu, Z.-R. *Synth. Commun.* **1989**, *19*, 1801−1812. (c) Huang, Z.-T.; Wang, M.-X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1085−1090. (d) Zhao, M.-X.; Wang, M.-X.; Huang, Z.-T. *Tetrahedron* **2002**, *58*, 1309−1316.

(5) Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2087−2094.

(6) Nie, X.-P.; Wang, M.-X.; Huang, Z.-T. *Synthesis* **2000**, *10*, 1439−1443.

(7) (a) Gupta, A. K.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 284−286. (b) Huang, Z.-T.; Liu, Z.-R. *Chem. Ber.* **1989**, *122*, 95−100. (c) Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 321−326.

(8) Yu, C.-Y.; Wang, L.-B.; Li, W.-Y.; Huang, Z.-T. *Synthesis* **1996**, 959−962.

(9) Xu, Z.-H.; Jie, Y.-F.; Wang, M.-X.; Huang, Z.-T. *Synthesis* **2002**, 523−527.

(10) (a) Destro, R.; Cosentino, U.; Moro, G.; Ortoleva, E.; Pilati, T. *J. Mol. Struct.* **1989**, *212*, 97−111. (b) Wang, X.-J.; Zhu, M.-J.; Guo, F.; Liu, Z.-R.; Huang, Z.-T. *J. Struct. Chem.* **1991**, *10*, 103−105. (c) Jones, R. C. F.; Martin, J. N.; Smith, P.; Gelbrich, T.; Light, M. E.; Hursthouse, M. B. *Chem. Commun.* **2000**, 1949−1950. (d) Jones, R. C. F.; Dimopoulos, P. *Tetrahedron* **2000**, *56*, 2061−2074. (e) Sottofattori, E.; Anzaldi, M.; Balbi, A.; Artali, R.; Bombieri, G. *Helv. Chim. Acta* **2002**, *85*, 1698−1705.

(11) Huang, Z.-T.; Liu, Z.-R. *Synthesis* **1987**, 357−362.

10.1021/jo0515428 CCC: $30.25
Published on Web 10/19/2005

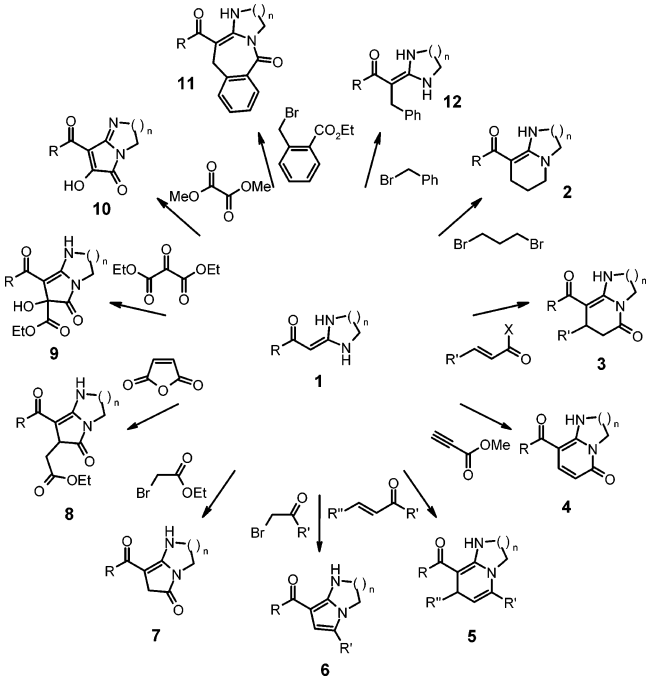
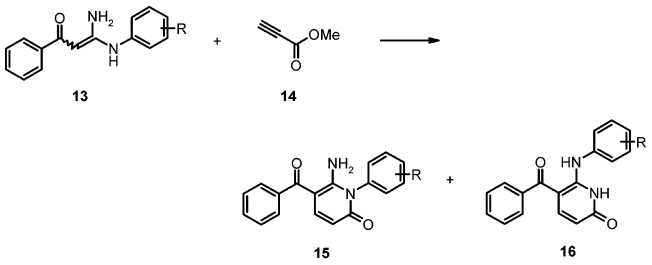


FIGURE 1. Heterocycles derived from cyclic ketene aminals.

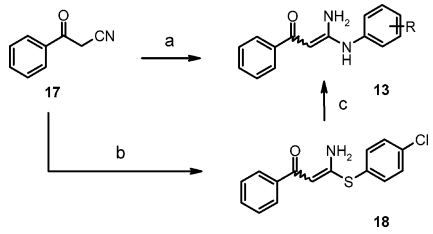
SCHEME 1. Reaction of Noncyclic Ketene Aminals 13 with Propiolic Ester 14



By the reaction of ketene aminals **1** with methyl propiolate, a pyridinone moiety is formed (Figure 1, **1** → **4**). An aza−ene mechanism has been proposed for this reaction.[3a,4c,5] However, it is difficult to rule out other pathways comprising a Michael addition[13] or a [2+2] cycloaddition with a subsequent rearrangement.

In connection with a recent medicinal chemistry program, we required a practical synthesis of 6-aminopyridinones of the generic structure **15** (Scheme 1).[14] Therefore, we envisioned the cyclization of mono-N-substituted ketene aminals **13** with propiolic acid methyl ester **14** to be a suitable route to the desired structures in analogy to the preparation of **4** (Figure 1). However, in contrast to the application of cyclic aminals **1**, very little is known about the reactivity of monosubstituted and therefore noncyclic ketene aminals of the generic structure **13**. Depending on the relative nucleophilicity of the primary compared to the secondary amino function, we expected mixtures of regioisomers **15** and **16**.

SCHEME 2. Preparation of Ketene Aminals[a]



[a] Reagents and conditions: (a) Corresponding aniline, salicylic aldehyde (cat.), piperidine (cat.), ethanol, reflux. (b) *p*-Chlorothiophenol, ethanol/chloroform, HCl (gas), rt. (c) Corresponding aniline, acetic acid, 80 °C.

Results and Discussion

Synthesis of Amino 2(1*H*)-Pyridinones. For the intended approach we desired a general and convenient method to the ketene aminals **13** allowing the incorporation of various anilinic residues. The synthesis of 3-amino-3-anilino-1-phenylprop-2-en-1-ones **13** in a single step from benzoylacetonitrile **17** and anilines in ethanol employing a catalytic system comprising salicylic aldehyde and piperidine has been described in the literature (Scheme 2, pathway a).[15] In our hands this procedure led to the desired ketene aminals **13** in satisfactory yields in several cases (Table 1, method A). However, the addition became very sluggish in instances of sterically hindered anilines bearing substituents in an ortho position (Table 1, **13x**) with the exception of electron-rich anilines such as 2,4-dimethoxyaniline (**13z**) and failed in the presence of certain functional groups such as hydroxyl groups (see **13r**). Literature precedent exists for an alternative two-step route leading to the same net product.[16,17] The required intermediate **18** was generated by nucleophilic addition of the thiophenol to the nitrile **17** in a mixture of diethyl ether and chloroform saturated with hydrogen chloride (Scheme 2).[18] The subsequent substitution with anilines was performed in acetic acid at 80 °C. This protocol proved to be a robust and reliable method to generate the ketene aminals **13**. It was done easily in high yields even on a multigram scale and tolerated numerous functional groups on the aniline, such as ethers, thioethers, amines, amides, phosphonates, carboxylic esters, alcohols, and phenol moieties (Table 1, method B). The sterically hindered ortho-substituted anilines such as *o*-methyl- (**13x**), *o*-isopropyl- (**13y**), and

(12) Li, Z.-J.; Smith, C. D. *Synth. Commun.* **2001**, *31*, 527−533.

(13) Knölker, H.-J.; Boese, R.; Hitzemann, R. *Heterocycles* **1989**, *29*, 1551−1558.

(14) The synthesis of 6-amino-5-benzoyl-4-methyl-1-phenylpyridin-2(1*H*)-one was described in the following: Wardakhan, W. W.; Agami, S. M. *Egypt J. Chem.* **2001**, *44*, 315−333.

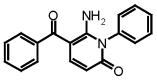
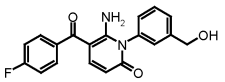
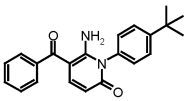
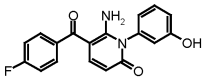
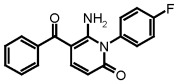
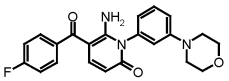
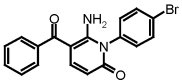
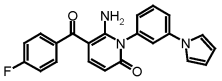
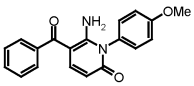
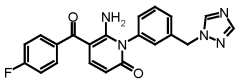
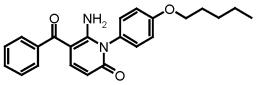
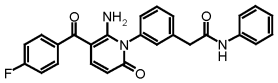
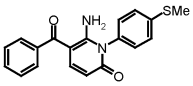
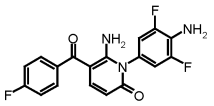
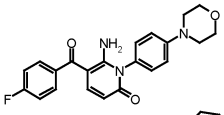
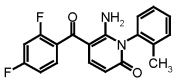
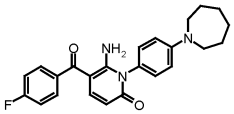
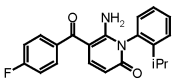
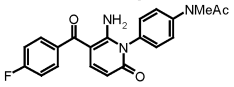
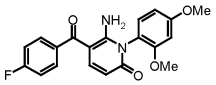
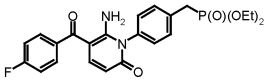
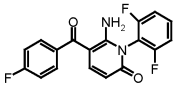
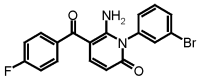
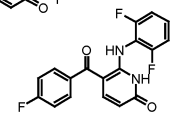
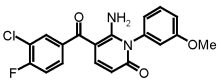
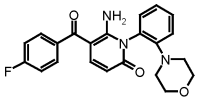
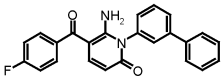
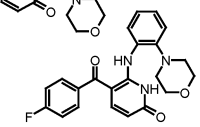
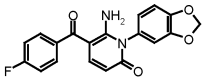
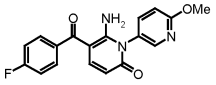
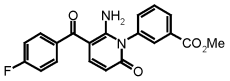
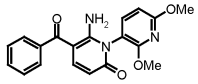
(15) (a) Krishnamurti, P. *J. Chem. Soc.* **1928**, 415−417. (b) Veer, W. L. C. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1118−1121.

(16) (a) Meier, E.; Glockner, H.; Kuffner, K.; Boie, I. *β*-Amino-*β*-imino acid esters. British Patent DT 1,409,987, Jan 31, 1974. (b) Todo, Y.; Yamafuji, T.; Nagumo, K.; Kitayama, I.; Nagaki, H.; Miyajima, M.; Konishi, Y.; Narita, H.; Takano, S.; Saikawa, I. Nicotinic acid derivatives. U.S. Patent 4,851,535, Jul 25, 1989.

(17) An alternative synthesis was published in the following: Woodman, D. J.; Murphy, Z. L. *J. Org. Chem.* **1969**, *34*, 3451−3456. For further methods for N,N′-disubstituted ketene aminals from activated methylene compounds and isothiocyanates, see: (a) Barun, O.; Ila, H.; Junjappa, H.; Singh, O. M. *J. Org. Chem.* **2000**, *65*, 1583−1587. (b) Shi, Y.; Zhang, J.; Grazier, N.; Stein, P. D.; Atwal, K. S.; Traeger, S. C.; Callahan, S. P.; Malley, M. F.; Galella, M. A.; Gougoutas, J. Z. *J. Org. Chem.* **2004**, *69*, 188−191 and references therein.

(18) The chloroform must be ethanol free. When ethanol-stabilized chloroform was used, the product contained a substantial amount of the ethyl imidoate. This compound was transformed into the desired amidine in low yield, see also ref 11 and Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449−8454.

TABLE 1. Isolated Yields of Ketene Aminals 13 and Cyclized Products 15

ketene aminal	yield[a]	structure **15**	prod.	yield[b]	ketene aminal	yield[a]	structure **15**	prod.	yield[b]
13a	18%[A]		**15a**	83%	**13q**	90%[B]		**15q**	52%
13b	86%[B]		**15b**	73%	**13r**	–[A] 83%[B]		**15r**	66%
13c	60%[A]		**15c**	96%	**13s**	85%[B]		**15s**	60%
13d	9%[A]		**15d**	65%	**13t**	82%[B]		**15t**	57%
13e	60%[A]		**15e**	84%	**13u**	73%[B]		**15u**	46%
13f	60%[B]		**15f**	60%	**13v**	29%[A]		**15v**	47%
13g	73%[B]		**15g**	58%	**13w**	68%[B]		**15w**	62%
13h	78%[A]		**15h**	64%	**13x**	–[A] 88%[B]		**15x**	67%
13i	73%[B]		**15i**	68%	**13y**	86%[B]		**15y**	37%[c]
13j	89%[B]		**15j**	65%	**13z**	80%[A]		**15z**	50%[c]
13k	54%[B]		**15k**	77%	**13aa**	73%[B]		**15aa**	43%
13l	71%[B]		**15l**	66%				**16aa**	4%
13m	–[A] 73%[B]		**15m**	50%	**13bb**	88%[B]		**15bb**	35%
13n	90%[B]		**15n**	65%				**16bb**	23%
13o	90%[B]		**15o**	77%	**13cc**	20%[A]		**15cc**	75%
13p	100%[B]		**15p**	80%	**13dd**	17%[B]		**15dd**	39%[c]

[a] Synthesis of the ketene aminal: Method A, directly from benzoylacetonitriles **17**; Method B, by substitution of *p*-chlorothiophenol. Cf. Scheme 2. [b] Cyclization in methanol with methyl propiolate at reflux for 1.5−3 h. Yields given are isolated yields. [c] Substantial amount of the regioisomer **16** was detected by HPLC but not isolated.

o-morpholinoaniline (**13bb**) yielded the desired aminals in almost 90% yield. Even the electron-poor 2,6-difluoro aniline derivative (**13aa**) was prepared in 73% yield using the two-step method. With 2,6-difluorobenzene-1,4-diamine we isolated exclusively the product resulting from the reaction of the less hindered 4-amino group (**13w**).

FIGURE 2. NMR data of the regioisomers **15** and **16**.

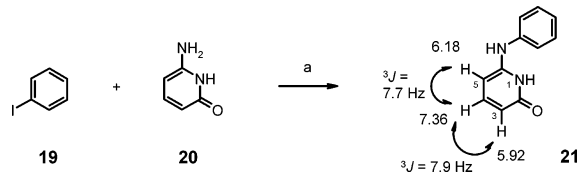
The subsequent cyclization of the aminals **13** with propiolic acid methyl ester **14** to the target pyridinones **15** was next investigated (Scheme 1). To the best of our knowledge, such asymmetric ketene aminal substrates have not been used in this reaction so far. However, similar reactions of cyclic ketene aminals[4] and phenylacetylimidazoles,[13,19] both containing two equivalent nitrogens, have been reported.[20] Alternatively to propiolic acid methyl ester **14**, propiolic acid with carbonyldiimadazole as activator is used very often.[3c,21]

On the basis of previous studies, cyclization of ketene aminals **13** was expected but with uncertain regioselectivity. We were then pleased to find out that heating of ketene aminal **13a** with methyl propiolate in methanol resulted in a single isolated compound in 83% yield. Many functional groups were compatible with the cyclization conditions, including alkyl, halogen, ether, and thioether moieties, amines, amides**,** carboxylates, phosphonates, alcohols, and phenols. However, if ortho-substituted anilines were built in the ketene aminal, the regioselectivity of the cyclization dropped. For example, the crude product of the cyclization of **13y** was a 4:1 mixture of regioisomers as determined by LC-MS. In some cases the minor component **16** was isolated for structure assignment. As such the 2,6-difluoro derivative **13aa** gave 43% of the desired compound **15aa** accompanied by 4% of its regioisomer **16aa**. The *o*-morpholino-substituted substrate **13bb** yielded a 3:2 mixture of regioisomers **15bb** and **16bb**.

The structures of the regioisomeric pyridinones **15** and **16** were unambiguously assigned by NMR after isolation of both compounds. Without exception, in compounds of general structure **15** the ^{1}H NMR signal of the 3-H next to the pyridinone carbonyl appears in the range of 5.65−5.74 ppm (Figure 2). The ^3J coupling constant (between 3-H and 4-H) was determined to be 9.6−9.8 Hz. For the corresponding regioisomers **16** the 3-H signal is shifted consistently downfield to above 5.9 ppm. Evidence for the correct assignment comes from the analysis of the model system **21** which was synthesized in a Goldberg reaction[22] from 6-aminopyridin-2(1*H*)-one **20** as depicted in Scheme 3. Its analogous proton produces a resonance peak at 5.92 ppm. Furthermore, the X-ray structure of **(*S*)-15z** confirmed this assignment (see Supporting Information).

Reaction Conditions and Product Distribution. During our investigations we studied the product distribution dependence on the reaction conditions, especially

SCHEME 3. Goldberg Reaction Leading to 6-Anilinopyridin-2(1*H*)-one 21[a]



[a] Reagents: (a) 0.05 equiv of CuI, 0.2 equiv of *trans*-1,2-diaminocyclohexane, 2.0 equiv of K_3PO_4, 35% yield.

SCHEME 4. Model System for Examination of the Reaction Conditions

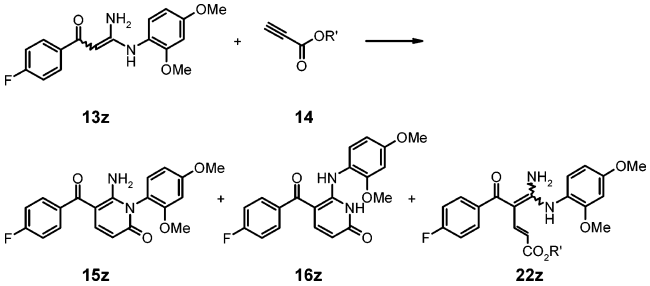


TABLE 2. Variations of the Reaction Conditions and Product Distribution (HPLC)

entry	solvent	temp., °C[a]	time, h	% **13z**	% **15z**	% **16z**	% **22z**
1	MeOH	65	2	2	60	13	16
2	MeOH	40	2	2	52	8	33
3	MeOH	rt	20	6	67	3	22
4	MeOH/H_2O (5:1)	40	4	2	69	4	25
5	MeOH/H_2O (5:1)	rt	24	2	78	2	18
6	EtOH	65	2	4	5	2	89
7	HOAc	65	2	63		8	
8	DMF	65	2	<5	3	3	84
9	EtOAc	65	2	15	1	1	83
10	DMSO	65	2	3	5	5	62
11	THF	65	2	4	1		95
12	acetone	65	2	4	1		95
13	toluene	65	2	4	2		94

[a] The reactions were performed with methyl propiolate (R′ = Me) on a 50 mg scale in sealed pressure test tubes. The temperature given is the temperature of the preheated oil bath.

the solvent. In a series of reactions using **13z** (Scheme 4) as a test system we analyzed the reaction mixtures by HPLC. After 2 h in refluxing methanol (Table 2, entry 1) we detected traces of starting material, 60% of the desired isomer **15z**, 13% of the regioisomer **16z**, and 16% of the noncyclized intermediate **22z**. As expected, the product distribution (**15z**:**16z** = 4.6:1 at 65 °C) was shifted to product **15z** when the reaction temperature was lowered to 40 °C (**15z**:**16z** = 6.5:1, entry 2). Running the reaction at room temperature resulted in a high regioselectivity of 22:1, but a 10-fold extended reaction time was needed to reach the same conversion (entry 3). The addition of water to the solvent had a beneficial effect. In a methanol−water mixture (5:1) the product distribution changed from 17:1 at 40 °C (entry 4) to 39:1 at room temperature with a prolonged reaction time (entry 5). Cyclization did not occur in other solvents. Even in ethanol instead of methanol we detected almost exclusively the intermediate product **22z** (entry 6). Similar results were obtained using dipolar aprotic solvents such as dimethylformamide, ethyl acetate, di-

(19) Dzvinchuk, I. B.; Vypirailenko, A. V.; Lozinskii, M. O. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2001**, *37*, 1096−1101.

(20) For a similar reaction of enaminones with propiolic ester leading to N-aryl pyridinones, see: Savarin, C. G.; Murry, J. A.; Dormer, P. G. *Org. Lett.* **2002**, *4*, 2071−2074.

(21) We reported on the application of in-situ-generated propiolic acid chloride in a similar reaction, see: Schirok, H.; Alonso-Alija, C.; Michels, M. *Synthesis* **2005**, in press.

TABLE 3. Influence of the Alcohol Residue in the Propiolic Ester on the Product Distribution[a]

entry	R′ (**14**)	% **13z**	% **15z**	% **16z**	% **22z′**
1	Me	<5	60	13	16
2	Et	<5	46	13	36
3	*i*Pr		33	34	17
4	*t*Bu	<5		24	56

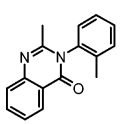
[a] All reactions were performed on a 50 mg scale in methanol at 65 °C for 2 h in sealed pressure test tubes.

methyl sulfoxide, tetrahydrofuran, and acetone (entries 8−12) and in toluene (entry 13). In the latter three solvents product **22z** was obtained in high purity. The vinylic coupling constant of 15.7 Hz in the ^{1}H NMR of **22z** proves the *E* configuration of the double bond α,β to the ester as depicted in Scheme 4. When **22z** was heated in methanol at 65 °C we obtained a 4.5:1 mixture of **15z** and **16z** very similar to entry 1. This shows that a facile *E*/*Z* isomerization must occur under the cyclization conditions. In acetic acid most of the starting material **13z** was not consumed (entry 7).

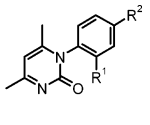
The influence of the alkyl group R′ in the propiolic ester **14** was also examined (Table 3). With ethyl instead of methyl propiolate as reagent a product distribution of **15z**:**16z** of 3.5:1 was found after 2 h at 65 °C in methanol (entry 2). In the case of isopropyl propiolate, a 1:1 mixture of **15z** and **16z** was obtained (entry 3). When *tert*-butyl propiolate was used, the cyclization step slowed significantly. In this case product **15z** was not detected (entry 4).

Atropisomerism and Absolute Configuration. For highly congested systems comprised of ortho-substituted aryl pyridinones, the question arose whether rotation around the C−N bond forming the biarylic axis was restricted. In the ^{1}H NMR spectrum of **15y** two doublet signals for the methyl groups of the *o*-isopropyl substituent appear at 1.09 and 1.19 ppm. Similarly, in the ^{13}C NMR spectrum the signals of the two methyl groups on the isopropyl moiety are distinguishable at 23.1 and 23.4 ppm. This pattern is characteristic for diastereotopic groups, thus indicating a stereogenic element in the molecule. In the case of a hindered rotation of the aryl ring around the inter-ring C−N bond, a stereogenic axis is defined by this bond, thus explaining the phenomenon through the existence of atropisomers. In the ^{1}H NMR of the *o*-morpholino compound **15bb** a similar effect is observed. The hydrogens of the morpholino group normally show up as two multiplets at 3.2 and 3.7 ppm, as, for example, in the meta-regioisomer **15s**. In case of the *o*-morpholino residue in compound **15bb** clearly resolved signals at 2.73 (2H), 2.87 (2H), and 3.48 (4H) ppm are observed.

The enantiomers of the ortho-substituted derivatives were separable by preparative chiral HPLC (**15y**, **15z**).[23] In the case of the meta-substituted analogue **15m** no separation was achieved at room temperature. Enantiopure **15z** was completely racemized in DMSO solution at 160 °C within 2 h. In boiling water the decrease of



23



24

FIGURE 3. Methaqualone **23** and 4,6-dimethyl-1-phenylpyrimidin-2(1*H*)-ones **24**.

the enantiomeric excess appeared to be much slower and could be followed accurately in a time frame of days.[24] For **15z** the half-life at 100 °C was determined to be 15 days. The energy barrier of rotation was calculated to be 139.0 kJ mol^{-1}, which corresponds to a half-life of 4050 years at room temperature.[25] This energy barrier is similar to that reported for **23** (131.6 kJ mol^{-1})[26] and **24** (114−126 kJ mol^{-1})[27] (Figure 3).

The absolute configuration of **(*S*)-15z** ($[\alpha]_D^{20.5} = -30.6°$, $c = 0.665$, DCM) was assigned by X-ray analysis (see Supporting Information).

Mechanism of Rotation. Rotational barriers may be resolved by computational approaches. Force fields, as used for **24** (R^1 = OMe, Figure 3),[27a] calculate only steric hindrance and neglect any stabilizing electronic effects. Pure ab initio Hartree−Fock as calculated for derivatives of **23** (Figure 3, HF/6-31G*)[26b] accounts for steric hindrance but neglects the electron correlation part of electronic interactions.[28] Quantitative values could be obtained by hybrid density functional or highly correlated ab initio methods but are not feasible due to computational limitations. We used semiempirical AM1 theory[29] to rank compounds qualitatively by relative barrier (VAMP6.5,[30] details are given in the Supporting Information).

From *o*-pyridine to *o*-isopropyl the barrier increases continuously with increasing size of the substituent. There is mostly no effect with introduction of a *p*-methoxy group and some lowering with introduction of a *m*-methoxy residue. The ranking is in line with the occurrence of separable enantiomers.

The coarse correlation between barrier heights and inter-ring dihedrals clearly suggests that electronic effects have only a negligible role compared with steric effects. Therefore, the question for the mechanism of

(22) (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (b) Li, C. S.; Dixon, D. D. *Tetrahedron Lett.* **2004**, *45*, 4257−4260.

(23) Column: KBD 6175, 250 mm × 20 mm. Eluent: isohexane/ethyl acetate 60:40. Temperature: 23 °C. Flow: 15 mL/min. UV detection: 254 nm.

(24) Time vs ee: 0 day, 98.2% ee; 2 days, 91.1% ee; 4 days, 79.7% ee; 7 days, 70.4% ee; 9 days 65.2% ee; 11 days, 59.3% ee; 14 days, 51.3% ee; 16 days, 47.0% ee; 21 days, 38.3% ee; 23 days, 33.2% ee. Linear regression of ln(ee(o)/ee) vs *t*: $y = 5.3423E-7$, $R^2 = 0.998$. $k = 2.671E-7$ [1/s]. $\Delta G^{\ddagger} = 139.0$ kJ mol^{-1}. $t_{1/2}$ (100 °C) = 15 days, $t_{1/2}$ (25 °C) = 4054 years.

(25) Ernst, L. *ChiuZ* **1983**, *17*, 21−30.

(26) (a) Mannschreck, A.; Koller, H.; Stühler, G.; Davies, M. A.; Traber, J. *Eur. J. Med. Chem. Chim. Ther.* **1984**, *19*, 381−383. (b) Azanli, E.; Rothchild, R.; Sapse, A.-M. *Spectrosc. Lett.* **2002**, *35*, 257−274.

(27) (a) Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1599−1602. (b) Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076−5080. (c) Sakamoto, M.; Utsumi, N.; Ando, M.; Saeki, M.; Mino, T.; Fujita, T.; Katoh, A.; Nishio, T.; Kashima, C. *Angew. Chem.* **2003**, *115*, 4496−4499; *Angew. Chem., Int. Ed.* **2003**, *42*, 4360−4363.

(28) (a) Göller, A.; Grummt, U.-W. *Chem. Phys. Lett.* **2000**, *321*, 399−405. (b) Göller, A.; Grummt, U.-W. *Chem. Phys. Lett.* **2002**, *354*, 233−242.

(29) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(30) Clark, T.; Alex, A.; Beck, B.; Burckhardt, F.; Chandrasekhar, J.; Gedeck, P.; Horn, A.; Hutter, M.; Martin, B.; Rahut, G.; Sauer, W.; Schindler, T.; Steinke, T. *VAMP 8.0*; Erlangen, 2001.

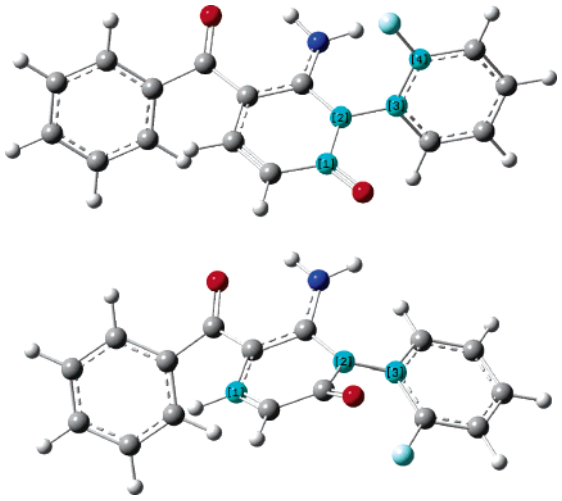


FIGURE 4. Ground-state and transition-state structures of **15a**, and the numbering schemes for the inter-ring dihedral C−N−C−C and out-of-plane deformation C−N−C (see Supporting Information).

rotation arises. While in the literature, on one hand, a pronounced C−N bond elongation for the transition states[27a] and, on the other hand, a 3,3-electrocyclic reaction with ring opening and closure has been suggested,[27b] we propose a different mechanism: The rotational barrier is significantly lowered by a pronounced deplanarization of the central pyridinone ring, thereby bending the rotating phenyl ring out of the plane in the one and the coplanar 1,3-amino carbonyl group in the other direction. The angles C−N−C (defined in Figure 4) for all compounds vary only slightly around 150°; for **15y**, with the highest barrier, it is 144°.

Synthetic Functionalization. As an additional aspect we became interested in the reactivity of the common core of the compounds and its compatibility with functional group interconversions. Concerning the amino group we knew from the X-ray structure as well as from the ^{1}H NMR spectra that a strong hydrogen bond toward the carbonyl oxygen is formed. We therefore questioned whether we could alkylate or acylate the amino function. Our attempts to benzylate or benzoylate the nitrogen failed. However, with the very reactive bromoacetic acid *tert*-butylester we were able to get the desired product **25** in 72% yield. The ester moiety was subsequently cleaved with trifluoroacetic acid almost quantitatively, and the resulting acid **26** was coupled to amides **27a**−**c** (Scheme 5).

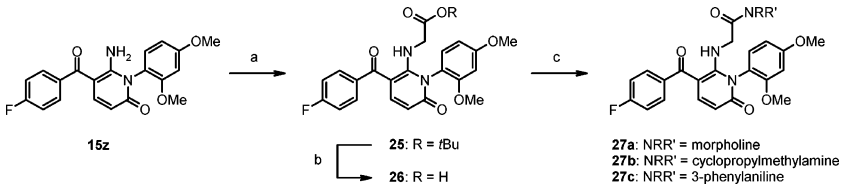
The low reactivity of the amino group encouraged us to evaluate transformations that are not compatible with a nucleophilic nitrogen. In this way we managed to mesylate the benzylic alcohol **15q** in the presence of the unprotected amino function in 89% yield. The resulting building block gave us access to a variety of benzylic amines **29a**−**c** (Scheme 6).

Amides may also be generated on a benzoic acid moiety. The acid **30** was liberated by hydrolysis of the methyl ester **15p** with lithium hydroxide in 96% yield. Starting with this benzoic acid, amides **31a**−**c** were generated in high yields with amines and anilines using polymer bound DCC and hydroxybenzotriazole. Dimer formation was not observed (Scheme 7).

Conclusions

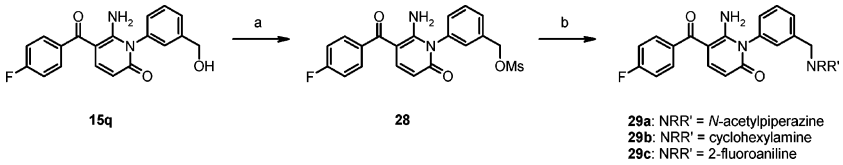
The cyclization of noncyclic ketene aminals of the general structure **13** with methyl propiolate in methanol provides a versatile short synthesis of 6-amino-5-benzoyl-

SCHEME 5. Derivatization of 15 with Bromoacetate[a]



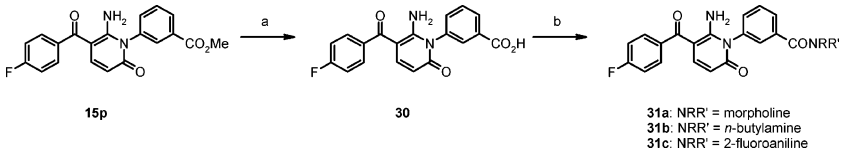
[a] Reagents and conditions: (a) *tert*-Butyl bromoacetate, K_2CO_3, acetone, reflux. (b) Trifluoroacetic acid, DCM, rt. (c) DCC, HOBt, DCM, DMF, corresponding amine, rt.

SCHEME 6. Alkylation of Mesylate 28[a]



[a] Reagents and conditions: (a) MsCl, TEA, DCM, 0 °C → rt. (b) Corresponding amine, THF, rt.

SCHEME 7. Syntheses of Amides 31[a]



[a] Reagents and conditions: (a) LiOH, methanol/water, 35 °C. (b) DCC, HOBt, DCM, DMF, corresponding amine, rt.

1-substituted 2(1*H*)-pyridinones **15** under mild conditions. The predominant product results from the reaction of the arylated nitrogen of the aminal. Only methanol or methanol/water mixtures were found to be suitable solvents for formation of the target compounds. As expected for a kinetically controlled product distribution, by lowering the reaction temperature from reflux to room temperature, the regioselectivity increases while the speed of the reaction slows down. The selectivity is also dependent on the size of the ester group. Presumably due to steric repulsion in the ring-forming step, the product distribution can be shifted to the isomeric product **16** with bulkier esters. In unsymmetrically ortho-substituted derivatives the barrier of rotation around the C−N-bond in the *N*-aryl pyridinones is high enough to isolate the atropisomers at room temperature. The experimental examination of the racemization reveals a barrier height of 139 kJ/mol for **15z**. We proposed a probable mechanism of rotation which comprises the deformation of the central pyridinone moiety in the transition state. The reactivity of the amino function is very low, allowing functional group interconversions which are normally not possible in the presence of an amino function.

Acknowledgment. We thank Dr. P. Schmitt, C. Streich, and D. Bauer for recording NMR spectra and helpful discussions. In addition, we are grateful to M. Stoltefuβ, G. Wiefel-Hübschmann, and S. Brauner for HRMS measurements.

Supporting Information Available: ORTEP-plot of **(*S*)-15z**; details on computations; experimental methods and compound data; ^{1}H and ^{13}C NMR spectra of compounds **15b**−**h**,**j**−**k**,**n**−**z**,**aa**,**bb**,**cc**, **18b**, **21**, **22z**, **25**, **26**, **27a**−**c**, **29a**−**c**, and **31a**−**c**; X-ray crystallographic data (CIF file) of compound **(*S*)-15z**. This material is available free of charge via the Internet at http://pubs.acs.org. The supplementary crystallographic data for this paper (CCDC 273344) can also be obtained free of charge via www.cc.dc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union road, Cambridge CB2 1EZ, U.K. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk).

JO0515428