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Mannich condensations of activated cyclic enamines

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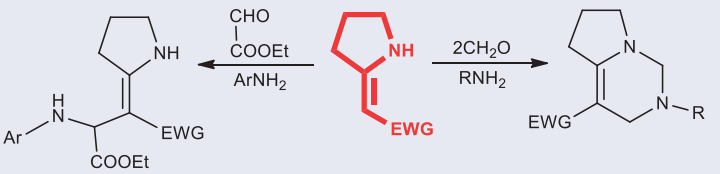
ABSTRACT

The synthesis of Mannich compounds starting from activated enamines, i.e., 2-nitromethylene-pyrrolidine and pyrrolidin-2-ylidene-acetic acid ethyl ester, with various amines and formaldehyde or ethyl glyoxylate are described. In order to furnish new Mannich type molecules and to improve the yields sequential reaction routes and 1,2,3-benzotriazole-substituted adducts as reactants were also tested. Additionally, the steric structure of a tricyclic spiro compound formed unexpectedly in high yield was elucidated in details by modern NMR methods.

GRAPHICAL ABSTRACT



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KEYWORDS
Benzotriazole auxiliary; Mannich reaction; one pot reactions; push–pull alkenes; pyrrolopyrimidines

Introduction

Push–pull enamines, enamines with an electron withdrawing group in the β-position, such as β-enaminonitriles,[1–6] β-enaminoesters,[7–13] or nitroenamines[14–21] are reactive intermediates in a large variety of reactions with different (ambident) electrophiles, such as α,β-unsaturated oxo-compounds, carboxylic acid chlorides, dicarbonyls,[22–24] or with 1,3-dipoles[25–27] resulting in biologically active bridgehead N-heterocycles and natural products, e.g., the extremely toxic marine alkaloid saxitoxin.[28,29]

The Mannich condensation is one of the most important and thoroughly studied multi-component reaction in synthetic chemistry affording a wide spectrum of valuable products used also in medicine. Push–pull enamines, particularly the representatives with cyclic structure, containing an active hydrogen at the nucleophilic β-carbon atom are suitable and often used components of these reactions.

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As many naturally occurring compounds contain a pyrimidine skeleton as a key structural motif, in the last two decades we witnessed to a tremendous increase of publications dealing with the synthesis of multi-functionalized dihydropyrimidines and tetrahydropyrimidines.[30–38] In this way, some cyclic enamines, such as 2-nitromethylene-pyrrolidine, -thiazolidine, -imidazolidine were already applied in Mannich reactions with formaldehyde and different amines affording fused tetrahydropyrimidines. In one of our previous papers [39] we described the Mannich reactions of 1-nitromethylenepyrrolidine (**1**) with aliphatic amines and formaldehyde. In two subsequent publications[18,30] we reported the Mannich reactions of **1** with ethyl glyoxylate and aromatic amines. The products obtained could be cyclized with formaldehyde to fused tetrahydropyrimidine derivatives.

In this present publication, we describe the synthesis of some new compounds starting from 2-nitromethylene-pyrrolidine (**1**) through double Mannich reactions with aromatic amines. Furthermore, we synthesized new Mannich products with pyrrolidin-2-ylidene-acetic acic ethyl ester (**2**) aiming to broaden the scope of application of such hitherto less studied enamines.

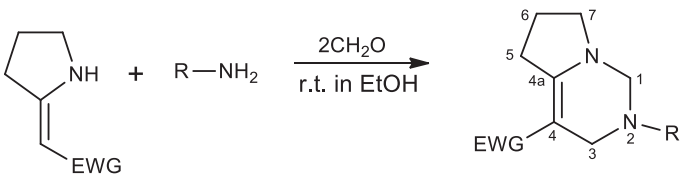
Results and discussion

Mannich reactions of enamines with formaldehyde and primary amines

In our previous work,[39] we reported the synthesis of Mannich products of **1** with different primary aliphatic amines and formaldehyde with good yields. In this article, we also describe the analogous reactions using aromatic amines (Scheme 1). In ethanol at room temperature, the reactions with anilines bearing electron-donating groups gave pyrrolopyrimidine derivatives **3** in good yields (Table 1). On the other hand, anilines with electron withdrawing substituent(s) exerting a strong deactivating effect did not react, and the formations of several unidentifiable products were observed.

In a similar procedure, enaminoester **2** was subjected to Mannich reaction.[40] Reacted with primary aliphatic amines and formaldehyde in the usual one pot protocol under mild conditions, it gave the analogous fused pyrimidine derivatives **4** in good yields (Scheme 1, Table 1)

Attempts to synthesize N-aryl derivatives using some selected aromatic amines were less successful. Under the same reaction conditions, only 4-methyl- and 4-methoxy-anilines gave the expected compounds **4j**, **4k** in poor yield. The numerous by-products of the complex reaction mixtures were not analyzed.



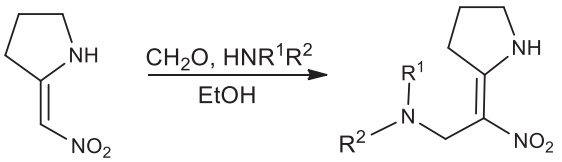
EWG		EWG	
NO_2	**1**	NO_2	**3**
COOEt	**2**	COOEt	**4**

Scheme 1. Preparation of pyrrolo-pyrimidines from enamines.

Table 1. Compounds prepared from enamines **1** and **2** in Mannich reactions.

Entry	EWG	R	Yield (%)
3a	NO_2	Ph	77
3b	NO_2	4-MePh	63
3c	NO_2	4-MeOPh	72
3d	NO_2	2-MeOPh	49
4a	COOEt	$CH(CH_3)_2$	82
4b	COOEt	$C(CH_3)_3$	61
4c	COOEt	CH_2Ph	42
4d	COOEt	2-MeOPhCH_2CH_2	64
4e	COOEt	3,4-MeOPhCH_2CH_2	77
4f	COOEt	cPentyl	68
4g	COOEt	cHexyl	70
4h	COOEt	N-Bn-piperidin-4-yl	58
4i	COOEt	N-Et-piperidin-3-yl	60
4j	COOEt	4-MePh	18
4k	COOEt	4-MeOPh	29

Reaction conditions: **1** or **2** (1.0 mmol), formaldehyde, in (2.5 – 3.0 mmol, 35% formaline), RNH_2 (1.0 mmol), in EtOH, 3–8 h stirring at ambient temperature.



1 **5**

Scheme 2. Mannich reaction of **1** with secondary amines.

These striking differences in reactivity of **1** and **2** can be explained with the stronger electron withdrawing ability of the nitro group and the stronger nucleophilic character of the aliphatic amines compared to the ethoxycarbonyl group and to the less basic aromatic amines, respectively.

Mannich reactions of enamines with formaldehyde and secondary amines using benzotriazole auxiliary

As we published[22,39] the nitroenamine **1** gave the expected Mannich products **5** with secondary amines in good yield (Scheme 2). On the contrary, in a usual one pot procedure and under same conditions the enaminoester **2** failed to furnish analogous products. Therefore, we attempted to follow a sequential route in preparation of Mannich products adapting the benzotriazole methodology. The benzotriazole-mediated approach in synthesis of diverse classes of organic compounds is well documented, particularly in the publications of the Katritzky's group.[41] As benzotriazole, this synthetic auxiliary, can be introduced and removed easily and can exert an activating effect during the synthetic operations, we applied it in a two-step approach.

Benzotriazole and aldehydes react reversibly to give addition products. These hydroxy compounds can react with amines under loss of water producing reactive species being in equilibrium with the benzotriazolate anion and the imminium cation (Fig. 1). These versatile intermediates in alkylation processes enable a significant extension of Mannich reactions, as well.

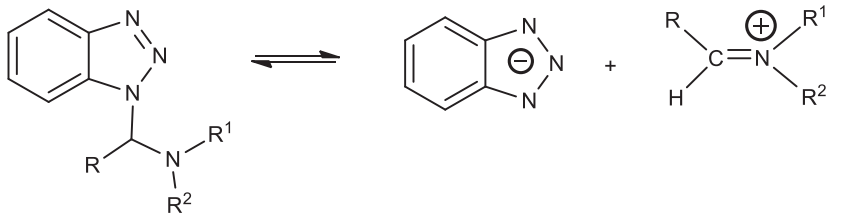
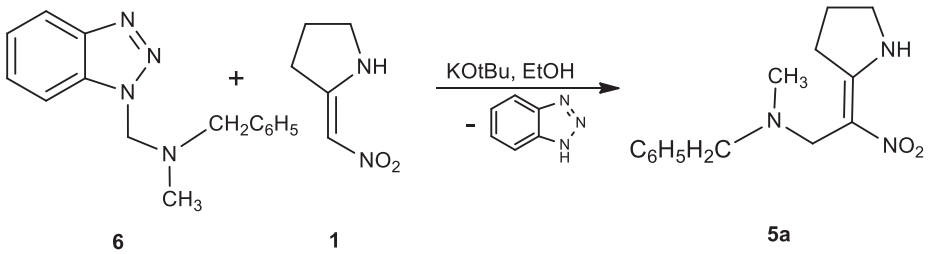
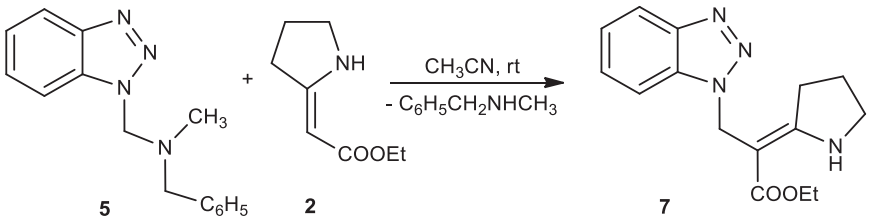


Figure 1. Dissociation equilibrium of benzotriazole-adducts.



Scheme 3. Reaction of the benzotriazole adduct **5** with nitroenamine **1.**

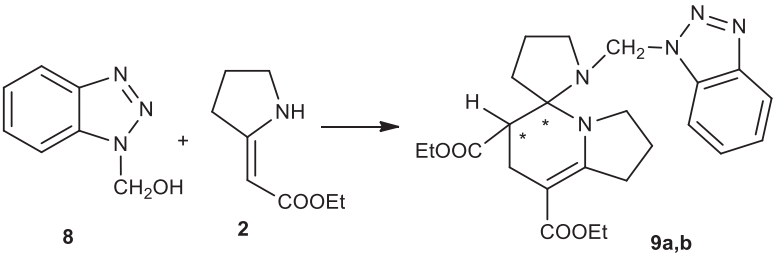


Scheme 4. Reaction of the benzotriazole adduct **5** with enaminoester **2.**

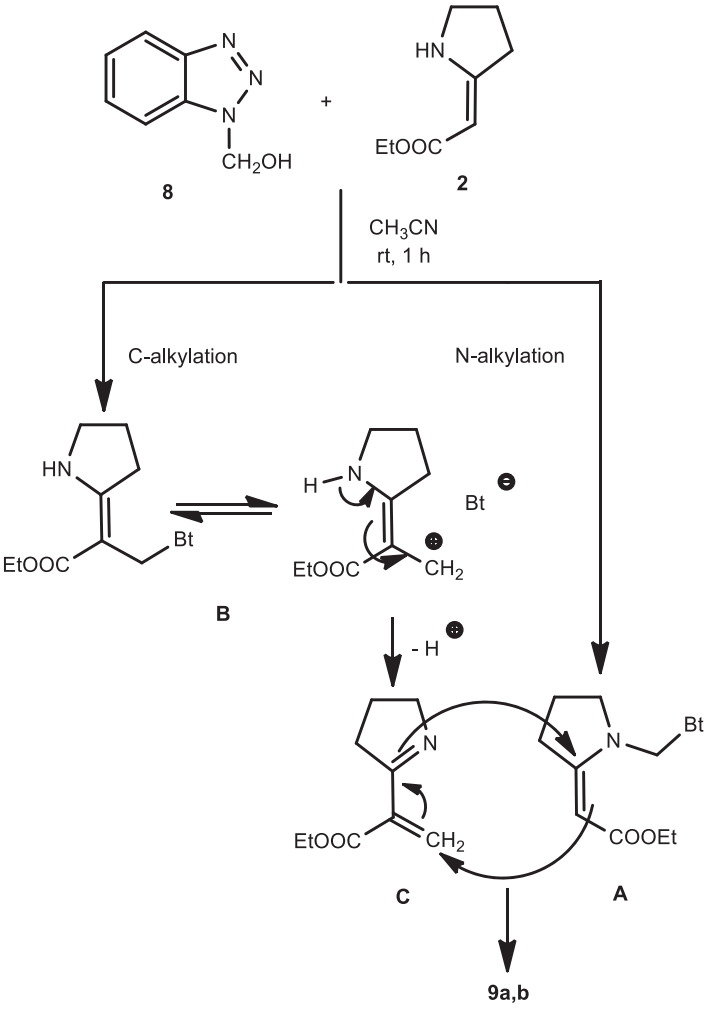
According to a known procedure[42] first we prepared compound **6** that incorporates the amine and formaldehyde components of our expected Mannich products. In the following step, we wanted to remove the benzotriazole auxiliary through the treatment with an enamine to result in the target compounds. This strategy worked well with 2-nitromethylenepyrrolidine, and gave **5a** in good yield as shown in Scheme 3. The product **5a** proved to be identical with the compound prepared in a one pot Mannich reaction of **1** with formaldehyde and N-benzylmethylamine as published previously.[39]

Next the above reaction was repeated with the enamino ester **2**. The desired product analogue to **6** was not formed, but, surprisingly, the N-benzylmethylamino group was removed to give **7** (Scheme 4).

As the above reaction reveals a strong affinity of the 1-benzotriazolylmethyl group to the nucleophilic carbon atom of the enamino ester **2**, a reversed sequence of the reaction steps was tested. Thus, 1-hydroxymethyl-benzotriazole[42] **8** and the enamino-ester **2** were allowed to react, attempting to obtain **7** directly and, afterwards, to remove the benzotriazolyl group in a treatment with an appropriate amine. This reaction, however, led to the diastereomeric spiro compounds **9a** and **9b** in high yield (Scheme 5).



Scheme 5. The unusual reaction of **8** with enaminoester **2.**



Scheme 6. Proposed mechanism for the formation of **9a,b.**

Their formation can be explained with a reaction cascade as follows (Scheme 6). It is supposed that the enamino ester **2** was N- and C-alkylated producing the intermediates **A** and **B** probably in a nearly 1:1 ratio. The 1,3-diene **C** can be derived from the equilibrium mixture **B** through the loss of a proton. **C** and **A** can interact in a 4 + 2 cyclization to provide the spiro compounds **9a,b**.

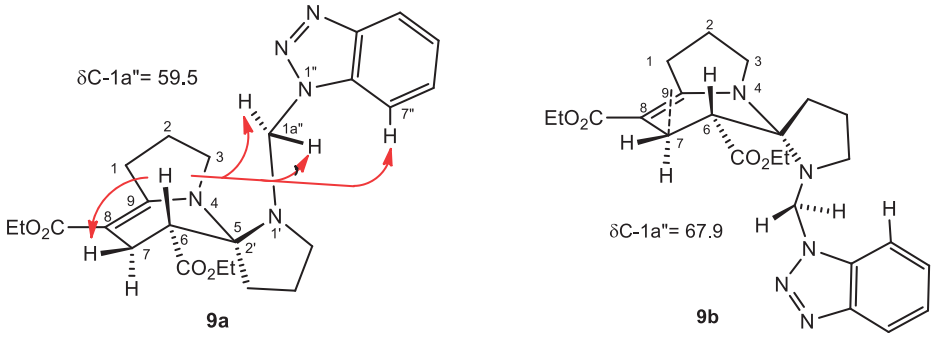


Figure 2. Structures of **9a** and **9b.**

The molecular ion [M^+] of **9**, formed by electron impact ionization, at *m*/*z* 453.2337 in its HR mass spectrum confirms the molecular formula $C_{24}H_{31}N_5O_4$ that is consistent with 12 double bond equivalents resulting in five rings and seven double bonds.

In the NMR spectra of the product **9** two series of signals were observed demonstrating the formation of two diastereomers **9a** and **9b** in a ratio of 91:9 determined by the signal intensities. Unfortunately, attempts to separate the diastereomers failed, after the numerous repeated recrystallizations practically no change in the above diastereomeric ratio was observed. The unfavorable interaction between the two bulky i.e., C(6)-COOEt and C(5)-benzotriazolylmethylpyrrolidino groups in **9b** can be considered as a plausible explanation for the high diastereoselectivity. The signal assignment of their ^{1}H and ^{13}C NMR spectra and their diastereomeric differentiation was achieved by different NMR techniques as follows. Noteworthy that the reaction had led to racemic mixtures of **9a** and **9b**, but, for the sake of simplicity only the enantiomeric forms with 6R configurations are depicted in Figure 2.

The identification and NMR signal assignment of 1-benzotriazolylmethylene and the two COOEt groups is trivial because there are no disturbing ^{1}H signals in the corresponding spectral range (see spectra in the Supporting material). The identification and separated detection of the ^{1}H signals of the two $-CH_2-CH_2-CH_2-$ spin-systems in the five-membered spiro- and also in the condensed ring was achieved with selective one-dimensional TOCSY experiments irradiating δHα-3 (2.91 ppm) and δHβ-3′ (2.24 ppm) signals, respectively. The HMBC correlations of H_2-C-1a″ hydrogen atoms with C-5′ (δC = 52.1 ppm) assigned the five-membered spiro ring. Irradiation of the Hβ-6 signal at 3.18 ppm (dd, J = 12.8 and 5.0 Hz) marked out the H_2-7 signals.

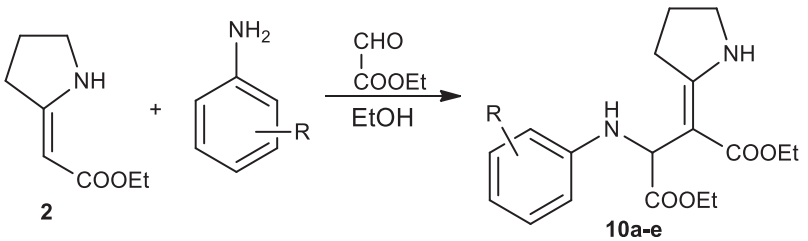
The 1-benzotriazolylmethylene moiety shows significantly different steric proximities in the major **9a** (5R6R) and the minor **9b** (5S6R) diastereomer. The high value of the J(Hβ-6, Hα-7) verifies the antiperiplanar arrangement of these hydrogen atoms, indicating the highly preferred envelope like conformation of the six-membered ring, in which the C-6 is the out of plane atom and the COOEt group occupies the α-equatorial position. In recognition of characteristic hydrogen-hydrogen spatial proximities, NOE experiments were particularly useful (as indicated with arrows in the Fig. 2). Irradiation of the Hβ-6 signal of **9a** at 3.18 ppm resulted in strong NOE responses on H_2-C-1a″, Hβ-7 and H-7″ hydrogen atoms proving the suggested structure unambiguously.

Although ^{13}C chemical shifts of **9a** and **9b** are rather similar, a significant difference is, however, observed only for the C-1a″ atom. Namely, this signal in **9a** exhibits a considerable diamagnetic shift of 8 ppm relative to that observed for **9b** (67.9 → 59.5 ppm). This strong downfield shift can be interpreted by the well-known γ–gauche effect between of H-C(6) bond and the C-1a″ atom. In **9b** there is no such spatial arrangement around C-1a″.

Reactions of enamines with anilines and ethyl glyoxylate

In an earlier publication,[18] we described the three component reactions of nitroenamine **1** with ethyl glyoxylate and various anilines. The products could be transformed with formaldehyde to versatile multisubstituted pyrrolopyrimidines. To broaden the scope of this procedure, we accomplished similar one pot reactions with enaminoester **2** (Scheme 7). The reactions were carried out at room temperature in ethanol resulting in compounds **10a–e**. The reaction times were 12–24 h, but the increase of the temperature led to a large number unidentified by-products. The yields with the nitroenamines are usually higher than with the enaminoester **2**, which can be explained with the stronger electron withdrawing effect of the nitro group. On the other hand, electron withdrawing substituents at the aromatic ring increase the reaction time. The yields are summarized in Table 2.

As we described earlier[18] on the basis of the HPLC measurements, it can be established that the three-component reaction takes place in two different ways. While electron donating substituents of the anilines facilitate the imine formation and the reaction with the enamine affords directly the product, electron withdrawing substituents slow down this reaction and the addition product of enamine and the aldehyde was formed predominantly, which can undergo to a nucleophilic substitution with anilines to give the desired products.

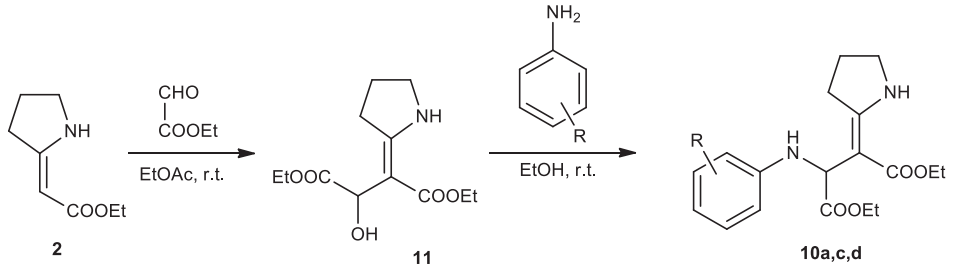


Scheme 7. One-pot reactions with enaminoester **2.**

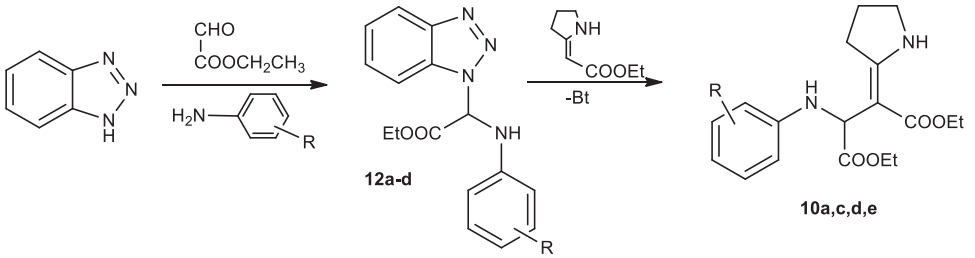
Table 2. Compounds **10a–e** prepared in one-pot reactions.

Product	R	Yield (%)
10a	H	30
10b	4-OMe	61
10c	4-F	57
10d	4-Me	36
10e	3-NO_2	31

Reaction conditions: **2** (1.56 mmol), $RC_6H_5NH_2$ (1.56 mmol), ethyl glyoxylate, (1.56 mmol, 50 w/w % toluene solution) in EtOH (4 mL), 3–8 h stirring at ambient temperature.



Scheme 8. Sequential reactions of **2** with ethyl glyoxylate and anilines.



Scheme 9. Benzotriazole mediated synthesis of **10a,c,d,e.**

Thus, we prepared the addition product **11** from enamine **2** with ethyl glyoxylate which was then converted to the desired products **10** with aromatic amines. In this way **10a**, **10c**, and **10d** were prepared, yields are 44, 68, and 52%, respectively (Scheme 8).

Attempts to prepare the Mannich products with aliphatic and alicyclic amines were unsuccessful because of the formation of a large number of unidentifiable by-products which can be explained with the lower stability of the imine intermediates.

In order to improve the yields of the three component reactions we attempted the use of the benzotriazole methodology. Benzotriazole adducts with ethyl glyoxylate and secondary amines were prepared several years ago by Katritzky et al. in benzene and used in alkylation reactions with organometallic reagents.[42]

First we prepared the benzotriazole adducts with different anilines and ethyl glyoxylate.[43,44] The reactions took place with 61–92% yields in EtOH at room temperature. The products **12a–d** crystallized from the reaction mixtures and could be used in the subsequent substitution without further purification. (Scheme 9, Table 3).

We hoped that enaminoester **2** will be a reactive CH-component in the nucleophilic displacement of the benzotriazole moiety (Scheme 9). The reactions were examined in different solvents, such as EtOH, polyethylene glycol (PEG 400), and water at room temperature. The expected compounds were obtained in most cases in 31–59% yields. The results summarized in Table 3 could be achieved in EtOH.

Materials and methods

General procedure for preparation of 3a–c

A solution of 1 mmol of 2-nitromethylene-pyrrolidine (**1**), 1 mmol of aniline or substituted aniline and 250 mg of formaline (35%, approx. 3 mmol of formaldehyde) in 3 mL of ethanol was stirred at room temperature for 3–8 h. The reaction was followed

Table 3. Compounds prepared *via* **12a–d** benzotriazolyl intermediates in EtOH.

Entry	R	Product	Yield (%)	Product	Yield (%)
1	H	**12a**	61	**10a**	59
2	4-F	**12c**	75	**10c**	57
3	4-Me	**12b**	71	**10d**	51
4	3-NO_2	**12d**	92	**10e**	31

Reaction conditions: for preparation of **12a,b,c,d**: $RC_6H_5NH_2$ (16.8 mmol), ethyl glyoxylate (16.8 mmol, 50 w/w % toluene solution), benzotriazole (16.8 mmol), in EtOH (20 mL), 3–8 h stirring at ambient temperature for preparation of **10a,c,d,e**: **12** (1.5 mmol), **2** (1.5 mmol), in EtOH (5 mL), 8–12 h stirring at ambient temperature.

by TLC. After completion the reaction mixture was cooled, and the crystalline product was filtered or evaporated and purified by column chromatography.

General procedure for preparation of 4a–k

A solution of 1 mmol of pyrrolidin-2-ylidene-acetic acid ethyl ester (**2**), 1 mmol of a primary amine, and 280 mg of formaline (35%, approx. 2.8 mmol of formaldehyde) in 3 mL of ethanol was stirred at room temperature for 3–8 h. The reaction was followed by TLC. After completion the solvent was removed at reduced pressure and the residue was purified with column chromatography on silica gel using hexane/*tert*-butylmethylether/*i*-propyl amine (50:45:5) as eluent.

Preparation of 5a

Benzotriazol-1-ylmethyl-benzyl-methyl-amine (**5**) (252 mg, 1.00 mmol), 2-nitromethylene-pyrrolidine (**1**) (128 mg, 1.00 mmol), potassium *tert*-butoxide (112 mg, 1.00 mmol) in EtOH (2 mL) was stirred for 5 h. After evaporation the orange red residue was mixed with water (2 mL) and extracted with EtOAc (2 × 2 mL). The EtOAc solution was dried (Na_2SO_4) and concentrated to yield a yellow viscous oil, that solidified upon standing (226 mg, 87%).

Preparation of 7

A mixture of 1-benztriazolylmethyl-benzyl-methylamine (504 mg, 2 mmol), enaminoester **2** (310 mg, 2 mmol) in acetonitrile (3 mL) was stirred at room temperature for 6 h. After removal of the solvent the yellow residue was crystallized from diisopropyl ether.

Preparation of 9

The dense white suspension of 1-hydroxymethyl-benztriazol (**8**) (273 mg, 1.83 mmol) and the enaminoester **2** (284 mg, 1.83 mmol) in acetonitrile (4 mL) was stirred at ambient temperature. After 2 h a colorless homogenous solution was obtained. Removal of the solvent gave a pale yellow oil that solidified upon cooling. Treatment with diisopropyl ether led to the formation of a white solid

General procedure for the synthesis of 10a–e with one pot reactions

The solution of ethyl glyoxalate (50% w/w toluene solution, 0.32 ml, 1.56 mmol), enamine **2** (242 mg, 1.56 mmol) and the corresponding aromatic amine (1.56 mmol) were dissolved in EtOH (4 mL) and stirred at room temperature until the starting materials were consumed. The solution was concentrated under reduced pressure and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (2:1) as eluent.

Preparation of 11

The solution of ethyl glyoxalate (50% w/w toluene solution, 0.61 ml, 3.0 mmol) and **2** (282 mg, 3.0 mmol) were dissolved in EtOAc (10.0 mL) and stirred at room temperature for 2 h. The solution was evaporated at reduced pressure, and the residue was crystallized from cyclohexane upon cooling.

General procedure for the synthesis of 10a, 10c, and 10d starting from 11

11 (232 mg, 1.5 mmol) and the corresponding aromatic amine were dissolved in EtOH (5 mL) and the solution was stirred for 8 h at room temperature. After completion of the reaction the solution was evaporated at reduced pressure and the residue was purified on silica gel using cyclohexane/ethyl acetate (2:1) as eluent. **10a**, **10c**, and **10d** were prepared, with 44, 68, and 52% yields, respectively.

General procedure for the preparation of 12a–d

The solution of ethyl glyoxalate (50% w/w toluene solution, 3.42 ml, 16.8 mmol), benzotriazole (2.0 g, 16.8 mmol) and amine (16.8 mmol) were dissolved in EtOH (20 mL), and stirred at room temperature until the starting materials were consumed. Upon cooling the product crystallizes from the solution.

General procedure for the synthesis of 10a, 10c, 10d, and 10e starting from 12a–d

12 (1.5 mmol) and **2** (1.5 mmol) were dissolved in EtOH (5 mL) and the solution was stirred for 8–12 h at room temperature. After completion of the reaction the solution was evaporated at reduced pressure and the residue was purified on silica gel using cyclohexane/ethyl acetate (2:1) as eluent.

Acknowledgments

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