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One-pot reactions of nitroenamines with anilines and ethyl glyoxylate

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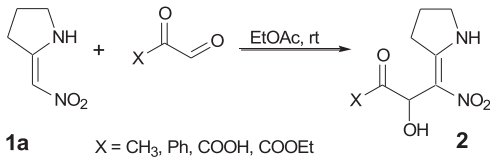
ABSTRACT

In a simple, one-pot, catalyst-free procedure starting from heterocyclic nitroenamines, substituted anilines and ethyl glyoxylate new ethyl 2-arylamino-3-nitro-propionates were prepared in good to excellent yields. Depending on the substituent pattern of the anilines applied, two routes for the one-pot reaction are suggested. Additionally, it was demonstrated that these multifunctional compounds of aza-Morita–Baylis–Hillman type were also formed in two-step protocols either from imines and nitroenamines or from the adducts of nitroenamines and ethyl glyoxylate with anilines.

1. Introduction

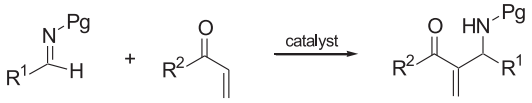
Push–pull enamines, enamines with an electron withdrawing group in the β-position, such as β-enaminonitriles,[1] β-enaminoesters,[2] or nitroenamines[3] proved to be valuable starting materials in the synthesis of various *N*-heterocycles in a number of cases. In one of our previous work we reported the reactions of 1-nitromethylenepyrrolidine (**1a**) with dicarbonyls.[4] Using methyl or phenyl glyoxal, glyoxylic acid and ethyl glyoxylate, the reaction took place smoothly at room temperature without catalyst to give the adducts **2** (Scheme 1). The reaction times were different, 12 h and 2 h for methyl and phenyl glyoxal, respectively, but only 10 min for glyoxylic acid and its ethyl ester.



Scheme 1. The reactions of nitroenamine with glyoxylates.

These results demonstrating the strong nucleophilic character of the β-carbon in push–pull alkenes prompted us to investigate the applicability of these reactive nitroenamines (e.g., **1a**) in similar reactions with imines, envisaging the formation of multifunctional adducts of aza-MBH type.

The aza-Morita–Baylis–Hillman (aza-MBH) reaction, particularly in the last decades, has become a very efficient, atom-economic and attractive method with enormous utility and synthetic potential.[5] The reaction takes place between an activated alkene and an imine in an addition–elimination sequence resulting in α-methylene-β-amino-carbonyl derivatives (Scheme 2).



Scheme 2. Formation of the aza-MBH adduct.

Many types of imines bearing different activating groups, such as sulfonylimines, in particular tosylimines[6] and also aryliminoacetates[7] have been developed and employed in the aza-MBH reaction with various activated olefins leading to the formation of densely functionalized valuable products that can be further applied in synthesis of a wide variety of compounds, useful in chemistry of natural products, plant protection and particularly in medicine and pharmaceutical industry. On the other hand, the

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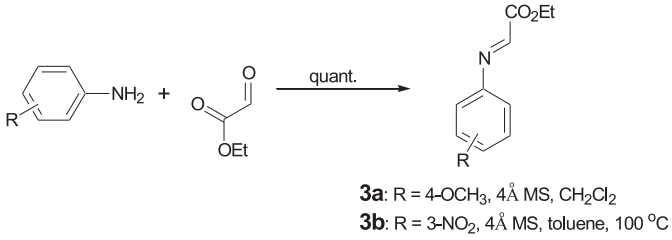
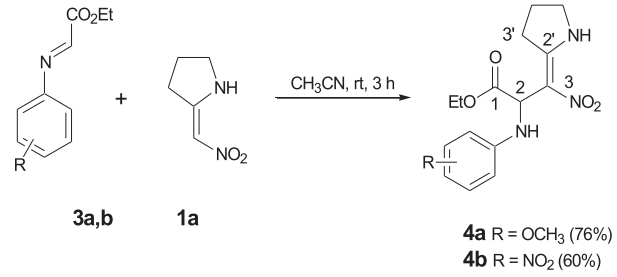
application of nucleophiles different from α,β-unsaturated ketones or esters, e.g., nitroenamines, is still not explored.

2. Results and discussion

First we prepared the imine **3a** from *p*-anisidine and ethyl glyoxylate according to literature procedure[8] in DCM at ambient temperature in the presence of molecular sieves with practically quantitative yield. The reaction of ethyl glyoxylate and 3-nitroaniline, however, took place only at elevated temperature in toluene to afford **3b** (Scheme 3). The aryliminoacetates **3a**,**b** thus obtained and used without further purification were then reacted with the nitroenamine **1a** resulting in the multisubstituted adducts **4a**,**b** (Scheme 4).



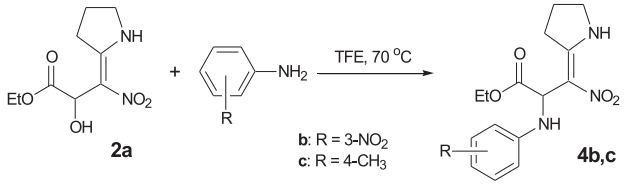
Scheme 3. Preparation of ethyl aryliminoacetates.



Scheme 4. Reaction of nitroenamine **1a** with aryliminoacetates.

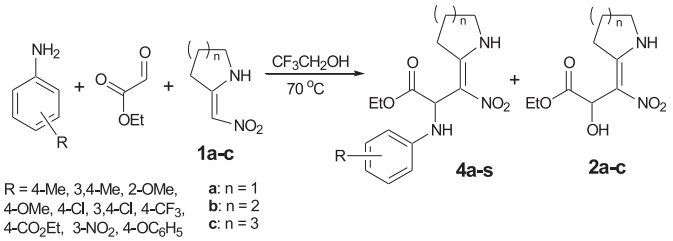
As the aza-MBH reactions are usually catalyzed by tertiary amines, the reaction was carried out in the presence of triethylamine or DABCO, as well. It was however established that neither the rate nor the conversion of the reactions was influenced by the base remarkably.

Our earlier results showed that the adduct **2a** underwent nucleophilic substitution with alcohols.[4] In an analogous transformation **2a** was converted into the substituted products **4b**,**c** using 3-nitro- and 4-methyl-anilines as nucleophiles. The reactions were carried out in different solvents, such as acetonitrile, ethanol, but the best results were achieved in trifluoroethanol. The reaction times were long in both cases, but after 48 h 87% conversion for **4b** and 76% for **4c** was detected (Scheme 5).



Scheme 5. Preparation of **4b**,**c** from **2a** and anilines.

As both approaches outlined above led to the same products, we attempted a one-pot procedure[9] (Scheme 6) instead of the sequential one. Indeed, the reactions of the nitroenamines **1a**–**c** with ethyl glyoxylate and anilines afforded the racemic products **4a**–**s** along with some **2a**–**c**.



Scheme 6. Three-component reaction with nitroenamines **1a**–**c**.

Based on NMR criteria, we reported[3c,4,10] previously the *Z* configuration of our starting compound **1a**. As this configuration may change under the reaction conditions applied, compound **4c** was subjected to selective NOE experiments. Upon irradiating the 2-H atom a significant NOE increment was detected on the signal of the 3′-H_2 atoms demonstrating their steric proximity and the unchanged *Z* configuration.

In a study of the solvent dependence the best yields (up to 80%) were observed in trifluoroethanol, mainly due to the distinguished physicochemical properties of fluorous solvents,[11] such as low nucleophilicity, high polarity and strong hydrogen bond donating ability. The reaction times were, however, strongly dependent on the nature of the substituent at the aromatic ring. The compounds prepared in the one-pot reaction are summarized in Table 1.

Table 1
Compounds **4a**–**s** prepared in one-pot reactions

Entry	R	*n*	Yield (%)	Reaction time
4a	4-OCH_3	1	67	4
4b	3-NO_2	1	77	48
4c	4-CH_3	1	72	2
4d	H	1	78	8
4e	2-OCH_3	1	66	4
4f	3-CH_3, 4-CH_3	1	66	4
4g	3-Cl, 4-Cl	1	72	24
4h	4-CF_3	1	69	48
4i	4-OC_6H_5	1	75	1
4j	4-$CO_2C_2H_5$	1	70	28
4k	3-CH_3, 4-CH_3	2	73	4
4l	3-Cl, 4-Cl	2	70	26
4m	3-NO_2	2	74	48
4n	4-$CO_2C_2H_5$	2	72	30
4o	3-CH_3, 4-CH_3	3	68	5
4p	3-Cl, 4-Cl	3	70	24
4r	3-NO_2	3	73	48
4s	4-$CO_2C_2H_5$	3	69	30

To get a deeper insight into the one-pot reaction, it was monitored by HPLC measurements. First we established that approximately 80% of the nitroenamine was consumed in 20 min in the three-component reaction of **1a** and ethyl glyoxylate with 3-nitroaniline, but only **2a** was formed (Fig. 1). Due to the electron withdrawing nitro group the formation of the imine **3b** is much slower than that of **2a**. The diagram for the same reaction on a longer time scale shows that **2a** was consumed slowly, to give finally compound **4b** (Fig. 2) with 81% conversion after 48 h.

On the other hand, an experiment with aniline bearing electron donating group at the aromatic ring gave different result. Using 4-methylaniline, nitroenamine **1a** was consumed in 1 h, and the ratio of the products **4c**/**2a** in the reaction mixture was 7:2, respectively. Consequently, the formation of the imine and next, the final