Improved Synthesis of Substituted Quinoxalines from New N=N-Polymer-bound 1,2-Diaza-1,3-butadienes

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Abstract: The first general protocol for the preparation of different N=N-polymer-bound 1,2-diaza-1,3-butadienes is reported. The utility of these supported reagents in the solid-phase in the preparation of 3-methyl quinoxaline-2-carboxylates by reaction with aromatic 1,2-diamines is presented.

Key words: 1,2-diaza-1,3-butadienes, hydrazones, Michael addition, quinoxalines, solid-phase synthesis

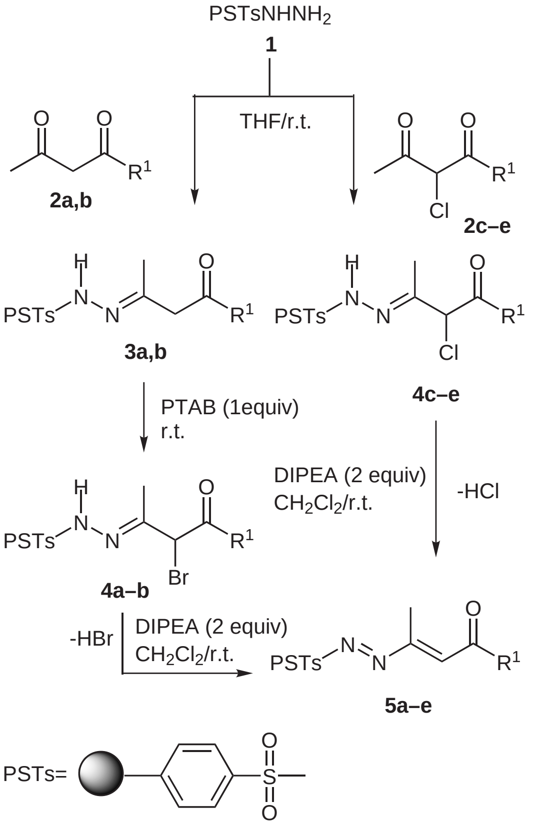
1,2-Diaza-1,3-butadienes are powerful tools in organic synthesis, particularly in the construction of heterocyclic rings.[1–3] Recently, we reported their synthesis on solid phase, starting from polymer-bound β-ketoester and free hydrazine derivatives.[4,5] In this case, the coupling site with the resin was the ester group at position 4 of the azo-ene system.

In this report, we describe a new protocol to obtain new N=N-polymer-bound 1,2-diaza-1,3-butadienes. The methodology uses PS-Ts-NH-NH_2, a resin bound equivalent of *p*-toluenesulfonyl hydrazide, usually employed as a scavenger of aldehydes and ketones.[6] Such a resin is also potentially useful as a polymeric reagent: for example, its reaction with carbonyl compounds **2a**–**e** furnishes resin-bound α-alogenated sulfonyl hydrazones **4a**–**e**.

Two different routes are possible for this synthesis. When polymer-bound hydrazide **1** reacts with *i*-propyl or benzyl acetoacetate **2a**,**b**, the formation of corresponding polymer-bound hydrazones **3a**,**b** is observed. These are subjected to bromination with phenyltrimethylammonium tribromide (PTAB) in dichloromethane to permit the introduction of the leaving group at the α-position of the C=N function to give the pertinent polymer-bound hydrazones **4a**,**b**. On the other hand, the reaction of **1** with methyl or ethyl 2-chloroacetoacetate **2c**,**d** or 2-chloro-*N*,*N*-dimethyl-acetoacetamide **2e** directly provides the α-chloro-polymer-bound hydrazones **4c**–**e**.

Treatment of **4a**–**e** with diisopropylethylamine (DIPEA) in CH_2Cl_2 furnishes N=N-polymer-bound 1,2-diaza-1,3-butadienes **5a**–**e** (Scheme 1, Table 1).

In order to test the reactivity of these new polymer-bound compounds and considering that quinoxaline derivatives are attractive due to their wide range of biological activities,[7] we decided to submit 1,2-diaza-1,3-butadienes in solid-phase **5a**–**e** to treatment with aromatic 1,2-diamines **6a**–**c**.[8]



Scheme 1

Reaction occurs in tetrahydrofuran (THF) under reflux and gives directly free 3-methyl quinoxaline-2-carboxylates **9a**–**h** that were easily purified by chromatographic methods (Scheme 2, Table 2). The reaction takes place by the nucleophilic attack of an NH_2 group of compounds **6** at position four of the azo-ene systems with formation of 1,4 adducts **7**. Compounds **7** instantaneously result in further internal attack of the second amino group at the C=N-hydrazone group to give compounds **8** that, by loss of *p*-toluenesulfonyl hydrazide and subsequent aromatization, lead to a solution of the final products **9a**–**h**.

In conclusion, the procedure described herein represents one of the few examples reported in literature for the synthesis of quinoxaline derivatives in solid phase.[8,9]

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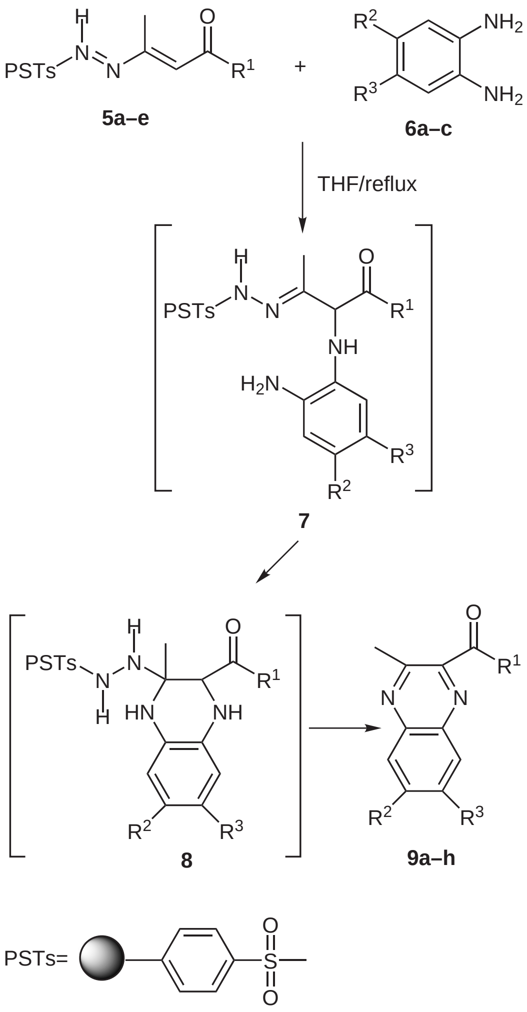


Scheme 2

In respect to our previous work in this field,[8] this new method simplifies the work-up procedure by avoiding the cleavage step and permits the introduction of different functional groups at position 2 of the quinoxaline system. Furthermore, in contrast with the article of Wu and Ede,[9] which reported the synthesis of a mixture of quinoxaline isomers, we obtained pure final products.

Typical procedure for the synthesis of polymer-bound α-bromo-hydrazones 4a,b

i-Propyl- or benzyl acetoacetate **2a**,**b** (5 equiv) were added to a magnetically stirred mixture of PS-Ts-NH-NH_2 **1** (0.500 g, 1.5 mmol per gram of resin) in THF (15 mL). The reaction mixture was allowed to stand at room temperature for 8–10 h, to give polymer-bound hydrazones **3a**,**b** that were washed with THF (5 × 10 mL) and CH_2Cl_2 (5 × 10 mL). To polymer-bound hydrazones **3a**,**b** in CH_2Cl_2 (150 mL) PTAB (1 equiv) was added portionwise with magnetic stirring. The reaction mixture was allowed to stand at room temperature for 4 h to give polymer-bound α-bromo-hydrazones **4a**,**b**, that were washed with THF (5 × 10 mL) and CH_2Cl_2 (5 × 10 mL).

Typical procedure for the synthesis of polymer-bound α-chloro-hydrazones 4c–e

Methyl or ethyl 2-chloroacetoacetate **2c**,**d** or 2-chloro-*N*, *N*-dimethyl-acetoacetamide **2e** (5 equiv) were added to a magnetically stirred mixture of PS-Ts-NH-NH_2 **1** (0.500 g, 1.5 mmol per gram of resin) in THF (15 mL). The reaction mixture was allowed to stand at room temperature for 5–10 h to give polymer-bound α-chloro-hydrazones **4c**,**d**, that were washed with THF (5 × 10 mL) and CH_2Cl_2 (5 × 10 mL).

Typical procedure for the synthesis of N=N-polymer-bound 1,2-diaza-1,3-butadienes 5a–e

To polymer-bound α-halogenated-hydrazones **4a**–**e** in CH_2Cl_2 (10 mL) was added under magnetic stirring DIPEA (2 equiv). The reaction mixture was allowed to stand at room temperature for 0.1 h to give N=N-polymer-bound 1,2-diaza-1,3-butadienes **5a**–**e** that were washed with THF (5 × 10 mL) and CH_2Cl_2 (5 × 10 mL).

Typical procedure for the synthesis of 3-methyl quinoxaline-2-carboxylates 9a–h

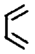
To N=N-polymer-bound 1,2-diaza-1,3-butadienes **5a**–**e** in THF (20 mL) 4,5-dimethylbenzene-1,2-diamine **2a**, benzene-1,2-diamine **2b** or naphtalene-2,3-diamine **2c** (3 equiv) were added. The reaction mixture was refluxed, with magnetic stirring, for 5–10 h furnishing 3-methyl quinoxaline-2-carboxylates **9a**–**h** in solution. The residue was washed with THF (5 × 10 mL) and CH_2Cl_2 (5 × 10 mL). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column (cyclohexane/ethyl acetate) to give **9a**–**h**, which were crystallized from diethyl ether/petroleum ether (40–60 °C).

Table 1 Reaction Times for the Synthesis of Polymer Bound α-Halogenated Hydrazones **4a**–**e** and Polymer-bound 1,2-Diaza-1,3-Butadienes **5a**–**e**

2	R^1	3	Reaction Time (h)	4	Reaction Time (h)	5	Reaction Time (h)
2a	*i*-PrO	**3a**	10.0	**4a**	4.0[a]	**5a**	0.1
2b	OBn	**3b**	8.0	**4b**	4.0[a]	**5b**	0.1
2c	OMe			**4c**	10.0	**5c**	0.1
2d	OEt			**4d**	5.0	**5d**	0.1
2e	$N(Me)_2$			**4e**	7.0	**5e**	0.1

[a] Reaction time for the bromination of **3a**,**b**.

Table 2 Yield and Reaction Time for the Synthesis of 3-Methyl Quinoxaline-2-carboxylates **9a**–**h**

5	R^1	**6**	R^2	R^3	**9**	Reaction Time (h)	Yield (%)
5a	O*i*-Pr	**6a**	Me	Me	**9a**	8.0	31
5b	OBn	**6b**	H	H	**9b**	7.0	28
5c	OMe	**6a**	Me	Me	**9c**	7.0	38
5c	OMe	**6b**	H	H	**9d**	5.0	24
5d	OEt	**6a**	Me	Me	**9e**	8.0	25
5d	OEt	**6b**	H	H	**9f**	6.0	27
5d	OEt	**6c**			**9g**	10.0	19
5e	$N(Me)_2$	**6b**	H	H	**9h**	5.0	15

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