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One-pot multicomponent synthesis of diazepine derivatives using terminal alkynes in the presence of silica-supported superparamagnetic iron oxide nanoparticles

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ABSTRACT

A new, efficient, one-pot multicomponent reaction for the synthesis of diazepine derivatives in excellent yields is described. The reactions of various 1,2-diamines, terminal alkynes, and an isocyanide take place in the presence of a catalytic amount of magnetically recoverable silica-supported superparamagnetic Fe_3O_4 nanoparticles in ethanol (as a green reaction medium) at ambient temperature.

Multicomponent reactions (MCRs) and sequential transformations offer significant advantages over conventional linear-step syntheses, by reducing time, and saving money, energy, and raw-materials, thus resulting in both economic and environmental benefits. Due to the unique reactivity of the isocyanide functional group, isocyanide-based MCRs (IMCRs) are among the most versatile in terms of the number and variety of compounds which can be generated.[1–3]

As a consequence of the advantages of monodispersed and size-controllable nanoscale magnetic materials, such as core/shell nanoparticles, highly functional materials with modified properties, techniques, and procedures for their production have advanced considerably. They have provided many exciting opportunities which have led to an active exploration of magnetic nanoparticles in a wide range of nanotechnology applications, in material chemistry and many other fields, such as electronics, biomedical, pharmaceutical, optics, and catalysis.[4]

Nanomaterials, especially metal nanoparticles (MNPs) and supported magnetic metal nanoparticles (S-MMNPs) have emerged as new classes of nanocatalysts. Some important features of these catalysts are simple separation using an external magnet without the need for filtration, high catalytic activity, and a high degree of chemical stability in various organic solvents.[5–8] Iron has a great deal to offer on the nanoscale, including very potent catalytic properties.[9]

Biological interest in diazepines has been extended to antibiotics,[10,11] cancer,[12] viral infection (HIV),[13–15] and cardiovascular disorders.[16,17] Figure 1 shows the structures of the commercial diazepine-core drugs diazepam (**1**), clobazam (**2**), and triflubazam (**3**). The 1,5-benzodiazepine core is found in compounds active against a variety of target types including peptide hormones (**4**),[18] interleukin-converting enzymes (**5**),[19] and potassium blockers (**6**).[17] Tetrahydro-1*H*-1,5-benzodiazepine derivatives with carboxamide substituents (**7**) are potentially important as therapeutic and prophylactic agents for diabetes, diabetic nephropathy, or glomerulosclerosis.[20,21]

In addition, diazepines are especially useful synthons for the rapid construction of heterocyclic systems due to the presence of a possible electrophilic C=N site. This structural feature could allow the diversity-oriented synthesis[22] of small libraries of diazepine-based compounds for pharmacological testing toward a wide range of biological targets.[23]

In the literature, the syntheses of diazepine derivatives are reported using variations of reagents and catalysts such as the condensation reaction of a 1,2-diamine with various ketones in the presence of ceric ammonium nitrate (CAN),[24] $Yb(OTf)_3$,[25] $Sc(OTf)_3$,[26] $SiO_2/ZnCl_2$,[27] and silica sulfuric acid,[28] with alkynoates in the presence of $Ga(OTf)_3$,[29] and also with terminal alkynes in the presence of $Hg(OTf)_2$.[30] In addition, examples of metal-free mild syntheses of diazepines have been disclosed in the literature.[31]

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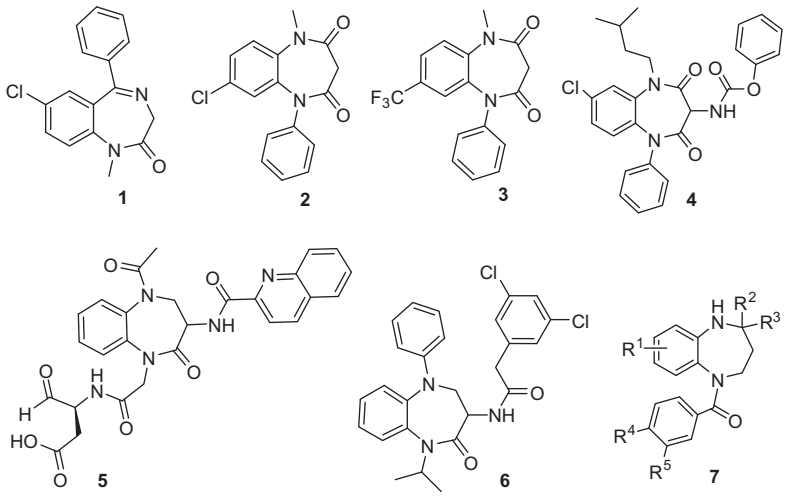


Figure 1. Some examples of medicinally and biologically important diazepine derivatives.

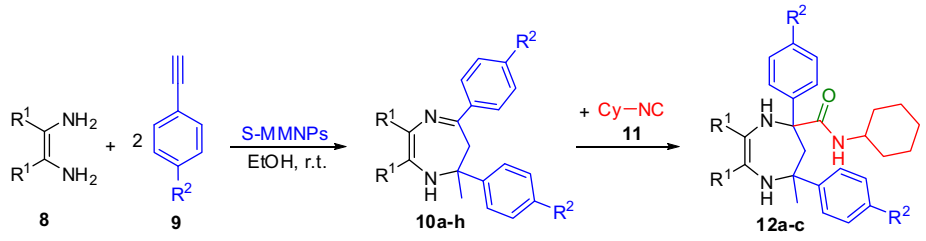
Due to the importance of the introduction of new, efficient, and inexpensive methods for chemical transformations, and also in continuation of our research on MCRs,[32–34] herein, a new approach for the one-pot multicomponent synthesis of diazepine derivatives **10a–h** and diazepine carboxamide derivatives **12a–c**, starting from simple and readily available substrates including 1,2-diamines **8**, terminal alkynes **9**, and isocyanide **11**, in the presence of a catalytic amount of silica-supported iron oxide (Fe_3O_4/SiO_2) nanoparticles (S-MMNPs) is reported. The reaction takes place in ethanol as a green reaction medium at ambient temperature (Scheme 1).

This method represents a useful extension of our previous work (Scheme 2),[32–34] where a carbonyl input, such as a cyclic or acyclic ketone, is replaced by a terminal alkyne.

To the best of our knowledge, this is the first synthesis of diazepines and diazepine carboxamides using terminal alkynes catalyzed by superparamagnetic MNPs via IMCRs. This new approach opens an important field involving the use of economically and environmentally efficient nanoscale magnetic materials in organic synthesis.

S-MMNPs were readily prepared according to the literature procedure,[4–8,34–36] by the addition of water-dispersed Fe_3O_4 nanoparticles into a basic solution of tetraethylorthosilicate (TEOS) and stirring overnight. Next, the resulting gel was heated for 30 min at 60 °C and the magnetic material was isolated by centrifugation, and dried under vacuum to give the S-MMNPs, which were stable under the employed reaction conditions.

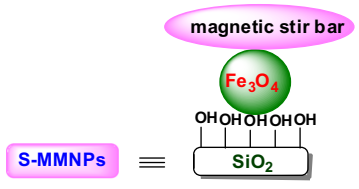
The particle size was studied by transmission electron microscopy (TEM) and the identification of the S-MMNPs was based on the analysis of TEM images. The obtained TEM images showed clearly monodispersed spherical-shaped nanoparticles in which the Fe_3O_4 nanoparticles were supported on silica (Fig. 2).



Product	R^1	R^2	Time (h)	Yield (%)
10a	CN	H	4	94
10b	CN	CH_3	5	95
10c	CN	Br	5	90
10d		H	4	92
10e		H	8	85 (95:5)[a]
10f		H	6	89
10g		CH_3	8	82 (88:12)[a]
10h		H	10	70 (96:4)[a]

Product	R^1	R^2	Time (h)	Yield (%)
12a	CN	H	6	90
12b	CN	CH_3	7	92
12c	CN	Br	7	83

[a] The regioisomeric ratio.



Scheme 1. Synthesis of diazepines **10a–h** and diazepine carboxamides **12a–c** in the presence of the supported Fe_3O_4/SiO_2 nanocatalyst.