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Perchloric Acid Supported on Silica Catalyzed Efficient Synthesis of 1,5-Benzodiazepines

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Abstract: Perchloric acid adsorbed on silica gel efficiently catalyzed the condensation of *o*-phenylenediamines (OPDA) with cyclic and acyclic ketones at ambient temperature to afford 1,5-benzodiazepines in good yields under solvent-free conditions.

Keywords: $HClO_4$-SiO_2, ketones, o-phenylenediamines

INTRODUCTION

Benzodiazepin and its derivatives constitute an important class of biologically active compounds showing remarkable therapeutic and pharmacological properties. They are extensively used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents.[1,2] In addition, 1,5-benzodiazepines also serve as key intermediates en route to a wide array of fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzdiazepines.[3] 1,5-Benzodiazepines are usually obtained through the condensation of *o*-phenylenediamines with ketones in the presence of BF_3-etherate,[4] polyphosphoric acid,[5] $NaBH_4$,[6] $MgO/POCl_3$,[7] metal triflates,[8] $InBr_3$,[9] and ionic liquid[10] and under microwave conditions.[11] However, many of these methods suffer from one or more disadvantages such as harsh reaction conditions, extreme temperatures,

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relatively long reaction times, use of toxic or expensive reagents, and occurrence of side reactions, which limit their use, especially in large-scale synthesis. As a consequence, there is need to find a simple, efficient, economical protocol for the synthesis of 1,5-benzodiazepines.

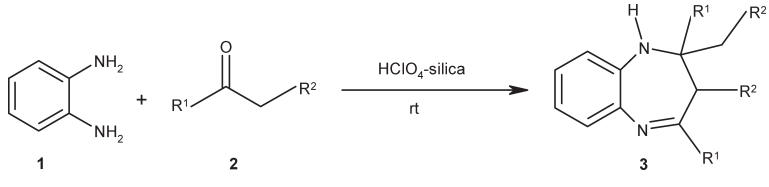
In recent years, heterogeneous catalysts have gained prominence because of environmental and economical considerations.[12] Recently, an interesting reagent, $HClO_4$ supported on silica gel, has been used as a stable and highly efficient catalyst in organic transformations.[13] This reagent is nontoxic, inexpensive, and environmentally acceptable. It also has excellent activity even on an industrial scale and in most cases can be recovered from reaction mixtures and reused. Because of its moisture insensitivity, ease of handling, and environmental friendliness, we disclose here the catalytic efficiency of $HClO_4$–silica for the synthesis of 1,5-benzodiazepines.

RESULTS AND DISCUSSION

The reaction of *o*-phenylenediamine (**1**) and acetone was carried out at ambient temperature in the presence of a catalytic amount of $HClO_4$-SiO_2 under solvent-free conditions. Complete conversion was achieved within 1 h to furnish 1,5-benzodiazepine **3a** in 92% yield (Scheme 1).

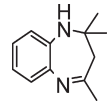
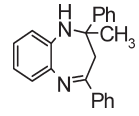
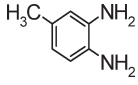
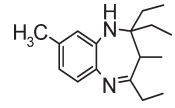
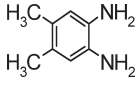
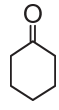
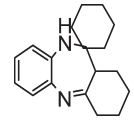
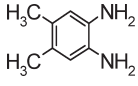
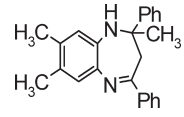
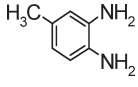
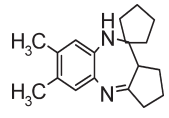
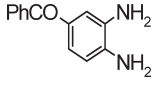
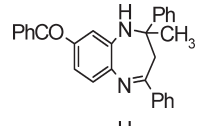
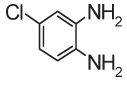
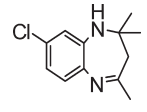
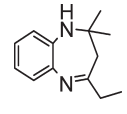
In a similar manner, electron-rich and electron-deficient *o*-phenylenediamines such as 4-methyl, 4,5-dimethyl, and 4-chloro reacted with various ketones to give the corresponding benzodiazepines in good yields under similar conditions. Our results are summarized in Table 1. After completion of reactions, it does not require any workup, as mere filtration of the catalyst is sufficient. The recovered catalyst can be reused at least four to five times with gradual decrease in activity. For instance, o-phenylenediamine with acetone gave 92, 88, 82, and 79% yields over four cycles. The crude products were purified either by recrystallization from n-hexane or by silica-gel column chromatography. However, the synthesis could not be achieved in the absence of catalyst.

The reactions are completed within 1.0–2.0 h and yields ranging from 78 to 95% depending upon the nature of the substrate. Cyclic ketones such as cyclohexanone and cyclopentanone also reacted well to produce the corresponding



Scheme 1.

Table 1. Synthesis of 1,5-benzodiazepinesa using $HCLO_4$-SiO_2

Entry	Diamine **1**	Ketone **2**	Product[a] **3**	Time (h)	Yield[b] (%)
a		CH_3COCH_3		1.0	92
b		$PhCOCH_3$		1.5	90
c		$CH_3CH_2COCH_2CH_3$		1.5	86
d				1.0	93
e		$PhCOCH_3$		2.0	79
f				1.5	95
g		$PhCOCH_3$		2.0	87
h		CH_3COCH_3		1.0	94
i		$CH_3CH_2COCH_3$		2.0	78

[a]All the products were characterized by ^1H NMR, mass, and IR spectra data.
[b]Isolated yields.

fused-ring benzodiazepines (entries d and f). In case of an unsymmetrical ketone such as 2-butanone, the ring closure occurs regioselectively from only one side of the carbon skeleton, giving a single product. The catalyst can be easily prepared[13a] and can be handled safely. The reaction conditions are mild so

that no side products or decomposition of the products are observed. All products were characterized by ^{1}H NMR, IR, and mass spectra and also confirmed by direct comparison with known compounds.[4–11] The reaction presumably proceeds via an intramolecular imine–enamine cyclization promoted by catalyst.

In summary, $HClO_4$-SiO_2 is found to be a new and highly efficient catalyst for the synthesis of 1,5-benzodiazepines. The notable advantages of this protocol, such as simplicity in operation, the low-cost catalyst, ease of handling, solvent-free conditions, high yields of products in short reaction times, and reusability of the catalyst make it a valuable alternative to the existing catalysts reported in the literature.

EXPERIMENTAL

IR spectra were recorded on either a Perkin-Elmer spectrophotometer or on the IR Nicole 740 FT-IR. ^{1}H NMR was recorded in Gemini at 200 MHz using TMS as an internal standard. M/s was recorded on a Micromass 7070 h or Finnigan Mat 1020 B mass spectrometer operating at 70 eV. Thin-layer chromatography (TLC) was done on precoated silica-gel-60f 254 (0.5-mm) glass plates.

General Procedure

To a stirred mixture of o-phenylenediamine (1 mmol) and ketone (2.5 mmol), $HClO_4$-SiO_2 (50 mg) was added at ambient temperature. After completion of the reaction, as indicated by TLC, the mixture was diluted with dichloromethane, and the catalyst was allowed settle down. Then reaction mixture was filtered, the catalyst was washed with dichloromethane, and the combined organic extract was dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (Merck, 100–200 mesh) ethyl acetate–hexane (1:9) to afford pure 1,5-benzodiazepine. The recovered catalyst was activated by heating at 80°C under vacuum for 2 h and reused.

SPECTRAL DATA FOR SELECTED COMPOUNDS

Spiro[cyclohexane-1,11′-(2′,3′,4′,10′,11′,11a′-hexahydro-1′*H*-bibenzo[*b*,*e*][1,4]diazepine)] (3d)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22–1.94 (m, 16H), 2.18 (s, 6H), 2.45–2.58 (m, 3H), 6.40 (s, 1H), 7.00 (s, 1H). IR (KBr): ν 3443, 2925, 1634, 1452 cm^{-1}. EIMS: m/z: 228 M^+.

2,2,4-Trimethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-8-yl Chloride (3h)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (m, 6H), 2.18 (s, 1H), 2.22 (s, 1H), 2.31 (s, 3H), 2.96 (brs, NH), 6.55–7.06 (m, 3H). IR (KBr): ν 3422, 2961, 1640, 1472 cm^{-1}. EIMS: m/z: 222 M^+.

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