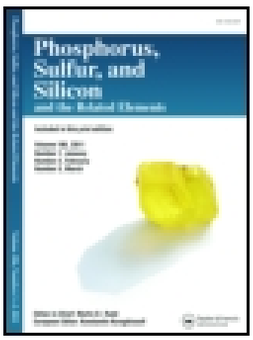

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Nano-TiO_2/SiO_2 catalyzed synthesis, theoretical calculations and bioactivity studies of new α-aminophosphonates

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Nano-TiO_2/SiO_2 catalyzed synthesis, theoretical calculations and bioactivity studies of new α-aminophosphonates

G. Sravya[a], Grigory V. Zyryanov[a,b], A. Balakrishna[c], K. Madhu Kumar Reddy[d], C. Suresh Reddy[d], G. Mallikarjuna Reddy[a,e], A. Camilo Jr.[f], J. R. Garcia[e], N. Bakthavatchala Reddy[a]*

[a]*Ural Federal University, Chemical Engineering Institute, Yekaterinburg, 620002, Russian Federation.*

[b]*I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Street, 620219 Yekaterinburg, Russian Federation.*

[c]*Rajeev Gandhi Memorial College of Engineering and Technology (Autonomous), Nandyal-518501, Andhra Pradesh, India.*

[d]*Department of Chemistry, Sri Venkateswara University, Tirupati-517 502, Andhra Pradesh, India.*

[e]*Department of Chemistry, State University of Ponta Grossa, Ponta Grossa, Parana, Brazil.*

[f]*Department of Physics, State University of Ponta Grossa, Ponta Grossa, Parana, Brazil.*

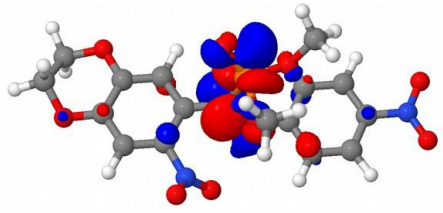
*For correspondence, e-mail: drbvreddyn@gmail.com

ABSTRACT

A simple and highly efficient method has been employed for the synthesis of a novel series of diverse biologically active α-aminophosphonates (**4a-m**) by reacting 7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (**1**) with various aromatic/hetero aromatic amines (**2a-m**) and dimethyl phosphite (**3**) by the Kabachnik-Fields reaction in the presence of an efficient heterogeneous Nano-TiO_2/SiO_2 (5 mol%) catalyst, which represents an effective Lewis acid and reusable catalyst under reflux conditions. A systematic structure activity

relationships (SAR) analysis was performed on all the title compounds to define a relationship between their chemical structures and their antimicrobial activities. In addition, theoretical calculations such as density functional theory (DFT) and minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were also evaluated.

Graphical Abstract



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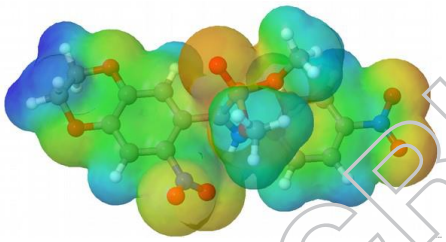

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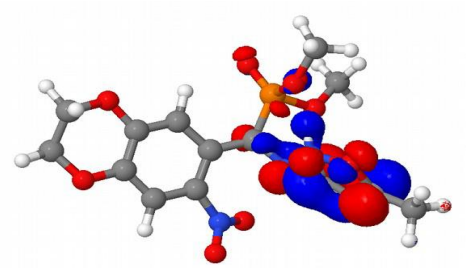
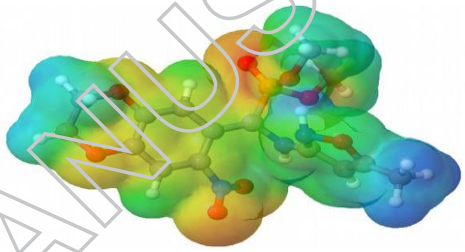


LUMO of 4j



MEP of 4j

KEYWORDS

Nano-TiO_2/SiO_2 catalyst; α-aminophosphonates; antimicrobial activity; SAR studies; Kabachnik-Fields reaction.

INTRODUCTION

Organophosphorus compounds play an important role in medicinal chemistry and occupy a central position in synthetic organic chemistry. Over the past few decades in the perspective of new drug discovery, α-aminophosphonates have attracted much attention due to the outstanding ability of the phosphonate moieties to act as biomimetics and pharmacophores. They have additional advantages such as low mammalian toxicity, easy decomposition, environmental compatibility and unique mode of action[1]. α-Aminophosphonates play a chief role in hapten design for antibody generation[2] and act as enzyme inhibitors[3], peptidomimetics[4], herbicides[5], insecticides[6], fungicides[7], antiviral agents[8]. Due to their importance, reviews[9-10] dealing with numerous synthetic methods have been published such as the use of ionic liquids as solvent[11], $\{Cu^{II}(NH_3)_3Cu^{I}(CN)\bullet[Cu^{I}(CN)_3]\}_n$[12], sulfated polyborate[13], nano-Gd_2O_3[14] and chitosan.[15] The α-aminophosphonates have also been synthesized in organic solvents by use of $SbCl_3/Al_2O_3$[16], $Cu(OTf)_2$[17], $BiCl_3$[18], $In(OTf)_3/MgSO_4$[19], GaI_3[20] as catalysts and also in the presence of Lewis-acid-surfactant-combined catalyst[21]. Specific synthetic cases even in solvent-free and catalyst-free conditions have also been reported[22]. However, these catalysts have some disadvantages. They require long reaction times, are moisture sensitive, require stoichiometric amounts of the toxic catalysts, give poor product yields, and generate large amounts of waste, which affects the quality of the reaction. It is a challenging goal to overcome these drawbacks.

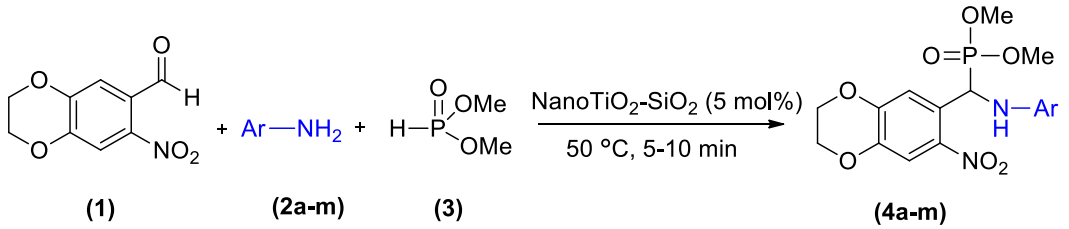
The use of solid acidic catalysts has gained importance in organic synthesis due to their robustness regarding operational simplicity, nontoxicity, reusability, low cost, and ease of isolation of products from the reaction mixture after completion of the reaction. Nano-TiO_2 has emerged as an efficient catalyst for various chemical transformations, e. g. the synthesis of quinoxalines[23], the preparation of diindolylmethanes[24], synthesis of xanthene derivatives[25] and β-acetamidoketones[26] Recently, the use of binary associate catalysts engrossed a great demand in synthetic aspects because of their wide scope and advantage of having large surface area. The advantages of using Nano-TiO_2 supported on SiO_2 as binary heterogeneous associate catalyst in synthesis is due to its readily availability, reusability and eco-friendliness. Nano-

TiO_2/SiO_2 has recently been used for photo degradation of new Fuchsin (C.I. 42520), Amaranth (C.I. 16185)[27] and photocatalytic oxidation of trinitrotoluene (TNT)[28].

The strategies for the synthesis of α-aminophosphonates may be variable[29-30]. Therefore, owing to our interest in the synthesis of biologically active molecular scaffolds of α-aminophosphonates, we have intended to develop the Nano-TiO_2/SiO_2 catalyzed synthesis of α-aminophosphonate derivatives from 7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (**1**), various aromatic/hetero aromatic amines (**2a-m**) and dimethyl phosphite (**3**) under neat conditions.

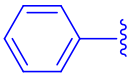
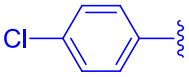
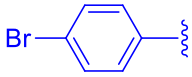
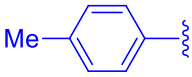
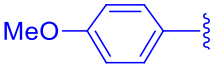
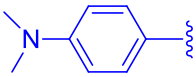
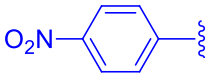
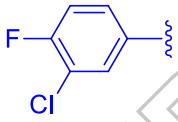
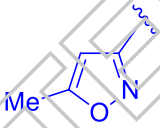
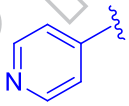
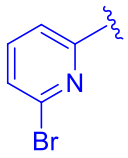
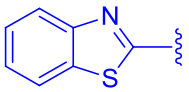
RESULTS AND DISCUSSION

We report an efficient and environmentally benign one-pot-three-component method for the synthesis of α-aminophosphonates (**4a-m**) by reaction of 7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (**1**), various amines (**2a-m**), and dimethyl phosphite (**3**) in the presence of Nano-TiO_2-SiO_2 as catalyst under neat conditions at 50 °C (**Scheme 1**).



Scheme 1: Nano-TiO_2-SiO_2 catalyzed synthesis of α-aminophosphonates (**4a-m**)

Table 1: Nano-TiO_2-SiO_2 catalyzed synthesis of α-aminophosphonates (**4a-m**)

Entry	Ar	Product	Time (min)	Yield (%)
2a		**4a**	5	94
2b		**4b**	7	90
2c		**4c**	7	90
2d		**4d**	5	91
2e		**4e**	5	95
2f		**4f**	5	97
2g		**4g**	8	90
2h		**4h**	6	86
2i		**4i**	5	84
2j		**4j**	7	84
2k		**4k**	8	92
2l		**4l**	5	89
2m		**4m**	10	91

In order to optimize the reaction conditions, the reaction between 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde, aniline, and dimethyl phosphite was taken as a model reaction. Initially, we carried out the model reaction at room temperature, but we observed only minimal formation of the corresponding α-aminophosphonates in the presence of Nano-TiO_2-SiO_2 catalyst even after 5 h of reaction time under solvent-free conditions (Table 1, Entry 1). By increasing of the reaction temperature from 30 °C to 50 °C the formation of α-aminophosphonates took place in 94% yield. A further increase of the temperature to 70 °C did not lead to an improvement of the yield.

The nucleophilic addition of phosphite to the resulting imine represents the key step in the one-pot synthesis of α-aminophosphonates. More recently, a number of conceptually different approaches have been developed for P-C bond formation in the synthesis of α-aminophosphonates, but catalytic approaches are of particular interest. We have studied different heterogeneous catalysts for this transformation (Table 2, entries 2-10). We found that 5 mol% of Nano-TiO_2-SiO_2 catalyst was sufficient for the completion of the reaction giving 94% product yield in 5 min. We observed that lower product yields (35%) in the absence of Nano-TiO_2-SiO_2 catalyst even after 5 h of reaction time (Table 2, entry 1). This shows that Nano-TiO_2-SiO_2 (5 mol%) is absolutely essential for the successful improvement of product yield of the reaction. It was noticed that less amounts of catalyst gave lower yields even after prolonged reaction time and higher utilization of mol % quantities also could not increase the product yield, but only decreases the reaction time. Survival of different functional substituents such as fluoro, chloro, bromo, methyl, methoxy, dimethylamino and nitro groups under these reaction conditions represents another important feature of this reaction, which made the synthesis of α-aminophosphonates with these functional groups possible and allowed to screen them for bioactivity in order to establish the relevant structural requirements for more potent bioactivity.

All synthesized compounds were characterized by FT-IR, ^{1}H, ^{13}C and ^{31}P NMR and all spectral data were in good agreement with the proposed structures.

DENSITY FUNCTIONAL THEORY (DFT) STUDIES:

In the present study, a systematic research on the possible minima of the SOMO and, LUMO energy, ionization energy, electron affinity, dipole moment and heat of formation (HF) was performed. We used the density-functional theory (DFT) for the calculation of the electronic structural orientation and frontier molecular orbitals location of α-aminophosphonates (**4a-m**).

The energies and electron densities of the frontier molecular orbitals, SOMO and LUMO, are important electronic parameters. The latter was used to determine the most reactive sites in the unsaturated system[36]. From Koopmans's theorem, the ionization potential (I) and electron affinity (A) can be expressed via HOMO and LUMO orbital potentials as $I = -E_{HOMO}$; $A = -E_{LUMO}$[37]. Our results also supported by this theorem in **Table 3**. On the other hand, dipole moments of the synthesized compounds varied from 8.42 to 2.00 Debye. Most of the active compounds had higher dipole moments. Compounds **4h** and **4j** were the most active compounds and also had higher dipole moments than other active compounds. However, compounds **4e** and **4g** had low dipole moments and were also comparatively biologically active. In fact, the other active compounds have different dipole moments with different bioassay activities. In addition, compounds with varying activities have a vast difference in their HF and hence we presume that there is no clear correlation between HF and biological activity.

In all synthesized compounds, the SOMO and LUMO orbitals were located differently and hence there was no proper correlation between the orbital orientation and the obtained biological results (Figure S 12).

According to the literature, compounds with higher biological activity are those with more negative LUMOs values in comparison to the less active compounds. Most active compounds can be distinguished clearly from less active compounds on the basis of their LUMO energies. According to our results, **4h** exhibiting an electron-withdrawing NO_2 group has a high negative LUMO energy value –1.37 eV and shows the highest antimicrobial activity. In addition, compound **4j** also displayed excellent antimicrobial activity due to its LUMO energy value of –1.13 eV. On the other hand, compound **4e** and **4g** have low LUMO values and were inactive. In spite of the least LUMO value of **4f**, it exhibited some biological activity. Other compounds showed moderate activity even though they possess different LUMO energy values. Finally, our detailed SAR studies demonstrated that compound **4h** and **4j** were the most biologically active compounds. This may be due to their high negative LUMO energy and dipole moment values.

CONCLUSION

The synthesis of a series of new α-aminophosphonates (**4**) by reacting 7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (**1**) with various amines (**2**) and dimethyl phosphite (**3**) using Nano-TiO_2-SiO_2 as a catalyst is reported. It is a simple, inexpensive and efficient method to obtain 55% to 94% yields. The reaction requires only 5 mol% of TiO_2-SiO_2 as reusable catalyst under solvent free conditions. The compounds synthesized exhibit outstanding anti-microbial/bacterial/fungal activities. Among them, **4h** was found to be highly active which showed an inhibition zone for significant anti-microbial activity of 34 mm at 100 µg/well with MIC and MBC values 6.25 and 12.5 µg/mL and showed excellent anti-fungal activity with an inhibition zone of 41 mm at 100 µg/well with MIC and MFC values 12.5 and 25 µg/mL. The results reveal that E_{HOMO} and E_{LUMO}, related to the electron donating ability, are the most important parameters for understanding the SAR bioactivity studies correlated with our title compounds **4a-m**.

EXPERIMENTAL

All reagents were purchased from Sigma-Aldrich, Hyderabad, India, and used without further purification. Melting points were determined on Guna Mel-Temp apparatus (Tempo Instruments and Equip., Mumbai, India) and were uncorrected. The IR spectra were recorded on a Bruker Alpha ECO-ATR FTIR (Attenuated total reflection-Fourier transform infrared) interferometer with single reflection sampling module equipped with ZnSe crystal. ^{1}H, ^{13}C and ^{31}P NMR spectra were taken on a Jeol JNM ECP 400 NMR instrument (Tokyo) at room temperature in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as internal standard. ^{31}P NMR (161.7 MHz) was taken in DMSO-d_6 using 85% H_3PO_4 as external standard with broadband ^{1}H decoupling. EI-Mass spectra were obtained on JEOL GCMATE II GC-MS spectrometer (Tokyo) at SAIF IIT-Madras, Chennai. Theoretical investigation of the α-aminophosphonates derivatives **4a-m** in the framework of Density Functional Theory (DFT) calculations were done applying B3LYP hybrid functional and 6-31 + G(p) basis set for C, Cl, F, H, N, O, S atoms and Sapporo Double Zeta Potential (SPK-DZP)[38] basis set for the Iodine atom, implementing on GAMESS-US[39] program package. The structure of compounds was full-relaxed in relation to the total energy of each system; while the electronic description was analyzed by means of SOMO (Single Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital), electron affinity energy (A, where $A = E^{-}-E^{0}$), ionization potential energy (I, where $I = E^{+}-E^{0}$) and molecular electrostatic potential (MEP). These electronic properties were calculated from total electronic energies of the neutral (E^{0}), cationic

(E^+) and anionic (E^-) models. The Supplemental Materials contains sample ^1H, ^{13}C and ^{31}P NMR spectra for products 4 (Figures S 3 – S 11).

General procedure for the synthesis of α-aminophosphonates 4a-m: A mixture of 7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (**1**), (1 mmol, 0.21 g), aniline (**2a**) (1 mmol, 0.09 mL), dimethyl phosphite (**3**) (1 mmol, 0.12 mL), and Nano-TiO_2/SiO_2 (5 mol%) were taken in a 10 mL round-bottomed flask, stirred at 50 °C for 5 min. After completion of the reaction, which was indicated by TLC, the mixture was washed with ethyl acetate (20 mL) to recover the catalyst by simple filtration. The solvent was evaporated under vacuum and the resulting crude product was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (1:1) as eluent to afford the pure product dimethyl (7-nitro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)(phenylamino)methylphosphonate **(4a)** (94%, Scheme 1). The same procedure was adopted for the preparation of all remaining title products (**4b-m**) by taking **2b** (0.09 mL), **2c** (0.13 g), **2d** (0.17 g), **2e** (0.10 g), **2f** (0.12 g), **2g** (0.14 g), **2h** (0.14 g), **2i** (0.15 g), **2j** (0.98 g), **2k** (0.94 g), **2l** (0.17 g) and **2m** (0.15 g), respectively.

The *Supplementary Material* file contains complete characterization data for the new compounds and selected spectra for **4a**, **4b**, and **4k** (Figures S3-S11).

Dimethyl (7-nitro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)(phenylamino)methane-phosphonate (**4a**): Brown solid; Yield 94%; mp 182-184 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 750 (P-$C_{aliphatic}$), 1230 (P=O), 3294 (NH); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.50 (d, 3H, $POCH_3$, J = 12 Hz), 3.74 (d, 3H, $POCH_3$, J = 8 Hz), 4.09 (s, 4H, OCH_2CH_2O), 4.64 (d, 1H, PCH, J = 20 Hz), 4.71 (s, 1H, NH), 6.52-7.11 (m, 7H, Ar-H); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ: 53.5 (2 × $POCH_3$), 63.6 (PCH), 64.5 (C-4 & C-5), 113.3 (C-2^1& C-6^1), 115.8 (C-6), 120.6 (C-4^1), 127.4 (C-3), 128.1 (C-1), 129.7 (C-3^1& C-5^1), 138.8 (C-2), 142.9 (C-7), 146.7 (C-1^1), 153.9 (C-8); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 21.4; EI-MS (*m/z*, %): 394 ($M^{+\bullet}$, 100); anal. calcd for $C_{17}H_{19}N_2O_7P$: C, 51.78; H, 4.86; N, 7.10; found C, 51.72; H, 4.81; N, 6.95.

Dimethyl (7-nitro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)(4-fluorophenylamino)methane-phosphonate (4b): Red solid; Yield 90%; mp 170-172 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 749 (P-$C_{aliphatic}$), 1245 (P=O), 3298 (NH); ^1H NMR (400 MHz, DMSO-d_6) δ: 3.48 (d, 3H, $POCH_3$, J = 12 Hz), 3.66 (d, 3H, $POCH_3$, J = 12 Hz), 4.21 (s, 4H, OCH_2CH_2O), 4.95 (dd, 1H, PCH, J = 12 Hz, J = 24 Hz), 6.21-6.25 (m, 1H, NH), 6.74-7.05 (m, 6H, Ar-H); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ: 52.9 ($POCH_3$), 53.2 ($POCH_3$), 54.8 (PCH), 63.9 (C-4 & C-5), 114.5 (C-3^1& C-

5^1), 114.8 (C-6), 115.5 (C-2^1& C-6^1), 124.9 (C-3), 129.4 (C-1), 132.8 (C-2), 143.8 (C-1^1), 145.7 (C-7), 152.9 (C-8), 154.5 (C-F,); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 21.2; EI-MS (*m/z*, %): 412 ($M^{+\bullet}$, 100); anal. calcd for $C_{17}H_{18}FN_2O_7P$: C, 49.52; H, 4.40; N, 6.79; found C,49.49; H, 4.38; N, 6.55.

Dimethyl (7-nitro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)(pyridin-4-ylamino)methane-phosphonate (4k): Green solid; Yield 92%; mp 136-138 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 746 (P-$C_{aliphatic}$), 1253 (P=O), 3300 (NH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.74 (d, 3H, $POCH_3$, J = 8 Hz), 3.90 (d, 3H, $POCH_3$, J = 8 Hz), 4.24 (s, 4H, OCH_2CH_2O), 4.62 (d, 1H, PCH, J = 12), 6.85-6.89 (m, 1H, NH), 7.26-8.21 (m, 6H, Ar-H); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ: 52.9 (P-OCH_3), 53.2 (P-OCH_3), 56.9 (P-CH), 63.9 (C-4 & C-5), 111.8 (C-2^1& C-5^1), 112.4 (C-6), 126.5 (C-3), 129.7 (C-1), 132.8 (C-2), 144.8 (C-7), 149.5 (C-3^1& C-4^1), 152.9 (C-8), 155.8 (C-1^1); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ: 23.5; EI-MS (*m/z*, %): 395 ($M^{+\bullet}$, 100); anal. calcd for $C_{16}H_{18}N_3O_7P$: C, 48.61; H, 4.59; N, 10.63; found C, 48.57; H, 4.52; N, 10.43.

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Table 1: Optimization of reaction conditions for the synthesis of 4a

Entry	Temperature (ºC)	Time (min)	Yield (%)[a]
1	30	300	40
2	40	10	72
3	50	5	94
4	60	10	94
5	70	5	94

[a]Isolated yields

Table 2: Influence of quantity of catalyst loading on the synthesis of α-aminophosphonates (4a-m)[a]

[a]Reaction of 7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (1 mmol), aniline (1mmol) and dimethylphosphite (1 mmol).

[b]Isolated yields.

Entry	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	No catalyst	300	35
2	Nano Gd_2O_3 (5)	120	55
3	Silica Supported Tungstic acid (5)	150	70
4	CAN-SiO_2 (10)	180	69
5	BF_3-SiO_2 (5)	210	80
6	Nano TiO_2-SiO_2 (1)	5	85
7	Nano TiO_2-SiO_2 (2)	5	89
8	Nano TiO_2-SiO_2 (5)	5	94
9	Nano TiO_2-SiO_2 (8)	5	94
10	Nano TiO_2-SiO_2 (10)	5	94

Entry	HF (Kcal/mol)	SOMO (eV)	LUMO (eV)	Dipole moment (db)	IP (eV)	EA (eV)
4a	-188.30840	-7.871	-0.850	3.14335	7.871	0.850
4b	-235.95359	-7.997	-0.956	4.24304	7.997	0.956
4c	-198.43560	-8.031	-0.969	4.60996	8.031	0.969
4d	-185.32465	-8.027	-0.963	4.48058	8.027	0.963
4e	-198.12019	-7.808	-0.820	2.85914	7.808	0.820
4f	-230.91687	-8.501	-0.603	4.82095	8.501	0.603
4g	-188.07994	-7.731	-0.790	2.00805	7.731	0.790
4h	-194.52765	-8.330	-1.378	7.85775	8.330	1.378
4i	-247.84993	-8.966	-0.887	4.59055	8.966	0.887
4j	-197.79121	-7.663	-1.132	8.42845	7.663	1.132

Table 3: Theoretical results of compounds (4a-m).

4k	-179.36649	-8.099	-0.968	4.93759	8.099	0.968
4l	-177.43448	-8.155	-1.053	4.94152	8.155	1.053
4m	-156.23057	-7.991	-1.113	3.50537	7.991	1.113