RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 57953

Received 8th October 2014
Accepted 17th October 2014

DOI: 10.1039/c4ra11961d

www.rsc.org/advances

Amphiphile catalysed selective synthesis of 4-amino alkylated-1*H*-pyrazol-5-ol *via* Mannich aromatization preferred to the Knoevenagel–Michael type reaction in water†

Atul Kumar,*[ab] Shivam Maurya,[ab] Maneesh Kumar Gupta[a] and Ratnakar Dutt Shukla[a]

An economic and efficient amphiphile (SDS) catalysed one pot synthesis of the aromatized 4-amino alkylated-1*H*-pyrazol-5-ol *via* a Mannich type reaction that is preferable compared to a Knoevenagel–Michael type reaction, *i.e.* aromatic aldehyde, secondary amine and 3-methyl-1-phenyl-5-pyrazolinone in water, has been developed. In this selective Mannich aromatization, the reaction proceeds *via* a micelle stabilized imine intermediate, followed by the nucleophilic addition of 3-methyl-1-phenyl-5-pyrazolinone and aromatization in water.

Pyrazole scaffolds have been considered as an important framework in pharmaceutical[1a,b] and agrochemical industries.[1c,d] Various pyrazole substructure derivatives find applications in therapeutical areas such as antimicrobials, anti-inflammatory agents, central nervous system, analgesics and oncology drugs. Various leading clinical and commercial drugs containing pyrazole include celecoxib[2a] (Cox-2 inhibitor), rimonabant[2b] (anorectic anti-obesity drug), PNU-32945 [2c] (HIV-1 reverse transcriptase inhibitor), Lonazolac[2d] (NSAID), and Zoniporide[2e] (NHE-1 inhibitor, Fig. 1). Pyrazole also acts as a constituent and receptor in transition metal[3a] and supramolecular chemistry,[3b] respectively. Therefore, identifying new approaches for the efficient synthesis of different pyrazole scaffolds with diverse substitution patterns is still a challenging task, involving various synthetic steps or multicomponent reactions.[3c,d]

Out of the various multicomponent reactions, Mannich reaction provides the most important and powerful synthetic methodology for the construction of novel diverse nitrogen containing biologically active organic scaffolds, that has been reported using organic solvent[4a,b] as well as in water.[4c,d]

Water, essential for life, is an ultimate green solvent involved in biochemical reactions; however, it is still not frequently used as a sole solvent for organic synthesis due to solubility issues as solubility is a prerequisite for reactivity. Using amphiphiles[5] is the best solution to overcome this problem. Amphiphiles not only provide a micellar lipophilic core for water insoluble organic reactants but also accelerate the reaction by micellar catalysis[6] in water.

One pot amphiphile catalysed Mannich aromatization, involving 3-methyl-1-phenyl-5-pyrazolinone, is still rarely mentioned in literature, whereas the Knoevenagel condensation followed by a Michael type addition of various nucleophiles or with itself is extensively reported.[7] Using this methodology, in 1959, Ahmed Mustafa *et al.*[8] reported the action of secondary amines on 1-phenyl-3-methyl-4-arylidene-5-pyrazolones and synthesized 4-amino aryl methyl-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**10**) in a moderate yield.

We wish to report here a highly efficient and economic procedure for the preparation of 4-amino alkylated-1*H*-pyrazol-5-ol derivatives *via* a one pot three-component Mannich type reaction, using amphiphile (SDS) in aqueous media in excellent yield (Scheme 1).

Our preliminary work has been based on organocatalysis as well as multicomponent reactions (MCRs) using a green approach for the synthesis of various biologically important heterocyclic compounds.[9] Inspired from this, we attempted to

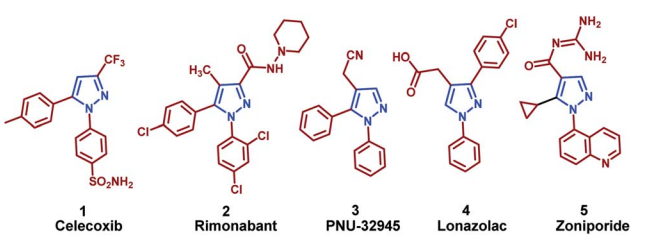
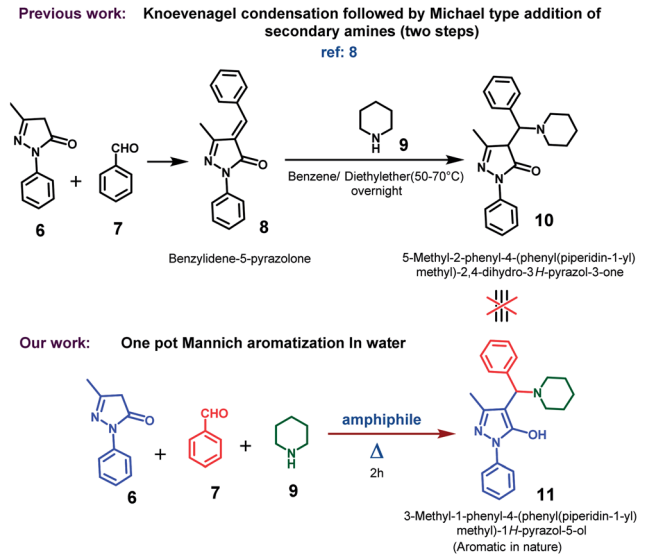


Fig. 1 Some pyrazole containing drugs.

[a]*Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Lucknow-226031, India*

[b]*Academy of Scientific & Innovative Research (AcSIR), New Delhi, India. E-mail: dratulsax@gmail.com*

† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra and Chiralpak IA HPLC for compounds. See DOI: 10.1039/c4ra11961d



Scheme 1

synthesize 4-amino alkylated-1*H*-pyrazol-5-ol derivatives using SDS in water.

Previously, in the absence of a catalyst, solvents using MeOH, EtOH, ACN, DMF, benzene, toluene afforded **8** [10a,b] efficiently. In heating conditions, dioxane, which is used as a solvent, also afforded **11a** in trace amount along with **8**. Considering this observation and in order to choose a better solvent–catalyst system, we carried out the reaction in dioxane by using a variety of catalysts (Table 1).

Starting from the catalytic amount of Brønsted acid using MSA and PTSA did not improve the yield of the desired product (**11a**). The bis-product[10c,d] (**12**) was obtained in this case as major product (Table 1, entries 1 and 2). All the non-metal/metal/heteropoly Lewis acids ($BF_3 \cdot Et_2O$, $FeCl_3$, $ZrCl_4$, copper(II) triflate, zinc(II) triflate and PMA) used in the reaction gave only bis-product (**12**) (Table 1, entries 3–8). The addition of catalytic amounts of silica-supported acids (SiO_2–Cl and $HClO_2$–SiO_2) was also not suitable for the reaction medium, affording bis-product (**12**) with trace amounts of **11a** (Table 1, entries 9 and 10). Moving towards the solid supported Brønsted acids (Cell SA, Star SA & SSA), eco-friendly and reusable catalysts also led the reaction to achieve bis-products very efficiently (Table 1, entries 11–13). However, when we carried out the reaction in water using DBSA (acting as surfactant as well as Brønsted acid) in heating conditions, surprisingly, we obtained the product (**11a**) in higher amounts (28%) compared to any another catalyst used (Table 1, entry 14).

This result encouraged us to optimize the reaction conditions by using a different type of amphiphilic surfactant to improve the yield of the desired product. In order to study the effect of surfactants (non-ionic, cationic, anionic), the reaction was carried out in water using benzaldehyde, 3-methyl-1-phenyl-5-pyrazolinone, and piperidine (summarised in Table 2).

Non-ionic surfactants (Triton-X-100, Tween 80, Tween 20 and Triton CF-10) were not found very effective and provided poor to average yield of the required product (41–53%) (Table 2, entries 1–4). It has been seen that in the case of non-ionic surfactants, on increasing the temperature, a decrease in head-group hydration occurs. Thus, these surfactants separate out as a pure phase from the aqueous solution, finally affecting the yield of the product. The product **11a** was also obtained, but in poor yield, when cationic surfactants like CTAB, TBAB and TBAF (acting as phase transfer catalysts[10e]) were employed (Table 2, entries 5–7). A Lewis acid surfactant, *i.e.* $Sc(DS)_3$, was also not suitable for the reaction medium (Table 2, entries 8). Fortunately, when we used SDS as an anionic surfactant in water, in heating conditions, both the yield and the reaction time were improved (Table 2, entry 9). However, the product formation and time factor were not adequate when SDS was employed at r.t. (Table 2, entry 13). Considering this observation, we increased the amount of SDS from 15 to 20 mol% and

Table 1 Effect of the catalyst on the synthesis of **11**[a,e]

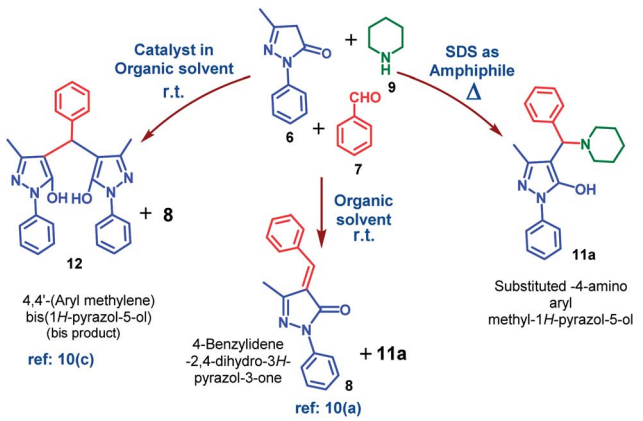
Entry	Catalyst[b]	Solvent	Yield of **12**/**8** (%)[c]	Yield of **11a** (%)[c]
1	MSA	Dioxane	60/18	12
2	PTSA	Dioxane	58/20	11
3	$BF_3 \cdot Et_2O$	Dioxane	59/24	—
4	$FeCl_3$	Dioxane	54/20	—
5	$ZrCl_4$	Dioxane	70/21	—
6	Copper(II) triflate	Dioxane	53/21	—
7	Zinc(II) triflate	Dioxane	57/22	—
8	PMA	Dioxane	70/11	—
9	SiO_2–Cl	Dioxane	52/24	Trace
10	$HClO_2$–SiO_2	Dioxane	62/22	Trace
11	CellSA	Dioxane	72/11	9
12	StarSA	Dioxane	70/12	10
13	SSA	Dioxane	74/10	9
14	DBSA[d]	Water	42/—	28

[a] Reaction conditions: the reaction was conducted with benzaldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolinone (1 mmol), piperidine (1.2 mmol) in solvent (2 ml) at r.t. [b] 10 mol% were used. [c] Isolated yield. [d] Reaction mixture was heated to 80 °C. [e] Abbreviations used in Table: MSA = Methane sulphonic acid; PTSA = *p*-Toluene sulfonic acid; PMA = Phosphomolybdic acid; CellSA = Cellulose sulphuric acid; StarSA = Starch sulphuric acid; SSA = Silica sulphuric acid; DBSA = *p*-Dodecylbenzenesulfonic acid.

Table 2 Effect of amphiphilic surfactants on the synthesis of **11**[a,i]

Entry	Surfactant[b]	Time (h)	Yield of **11a**/**12** (%)[c]
1	Triton X-100	8.5	53/trace
2	Tween 80	8.5	52/trace
3	Tween 20	8.5	48/trace
4	Triton CF-10	8.5	41/trace
5	CTAB	5.0	52/trace
6	TBAB	5.5	54/trace
7	TBAF	5.5	53/trace
8	$Sc(DS)_3$	6.5	41/12
9	SDS	2.0	68/—
10	SDS/PMA[d]	4.5	55/30
11	SDS/DBSA[d]	4.5	58/33
12	SDS/XSA[d]	4.0	57/27
13	SDS[e]	4.5	42/10
14	SDS[f]	2.0	52/—
15	SDS[g]	2.0	78/—
16	SDS[h]	2.0	91/—

[a] The reaction was conducted with benzaldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolinone (1 mmol), piperidine (1.2 mmol) in water (2 ml) at 80 °C. [b] 10 mol% were used. [c] Isolated yield. [d] 10 : 12 mol% were used. [e] The reaction was conducted at r.t. [f] 5 mol% catalyst. [g] 15 mol% catalyst. [h] 20 mol% catalyst. [i] Abbreviations used in Table: Triton-X-100 = $[C_{14}H_{22}O(C_2H_4O)_n]$ where n = 9–10; Tween 80 = Polyoxyethylene(20)sorbitanmonooleate (Polysorbate 80); Tween 20 = Polyoxyethylene(20)sorbitanmonolaurate (Polysorbate 20); Triton CF-10 = Benzyl-polyethylene glycol *tert*-octylphenyl ether; CTAB = Cetyltrimethylammonium bromide; TBAB = Tetra-*n*-butylammonium bromide; TBAF = Tetra-*n*-butylammonium fluoride; $Sc(DS)_3$ = Scandium tris(dodecyl sulphate); SDS = Sodium dodecyl sulphate; PMA = Phosphomolybdic acid; DBSA = *p*-dodecylbenzenesulfonic acid; XSA = Xanthan sulphuric acid.



Scheme 2

also decreased it to 5 mol% at 80 °C and, therefore, we demonstrated that the yield of product **11a** increased from 78% to 91% (Table 2, entries 15 & 16) and decreased to 52% (Table 2, entry 14), respectively. Moreover, we also employed the combination of anionic surfactant along with various acids by using SDS/PMA, SDS/DBSA and SDS/XSA (Table 2, entries 10–12) but the product formation was not satisfactory.

Therefore, SDS was proved to be the best amphiphile for the formation of substituted 4-amino alkylated-1*H*-pyrazol-5-ol derivatives using water as a solvent (Table 2, entry 16) (Scheme 2).

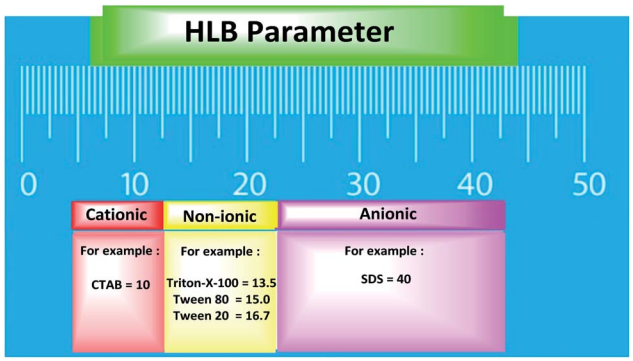
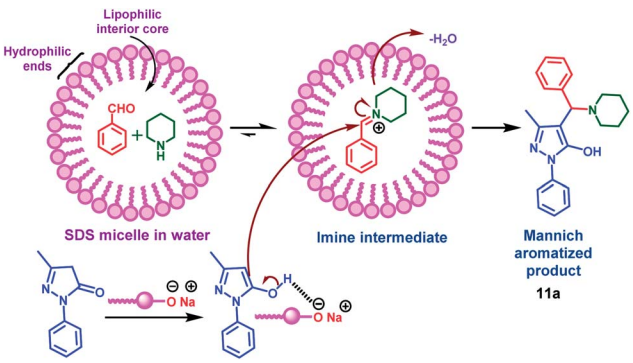
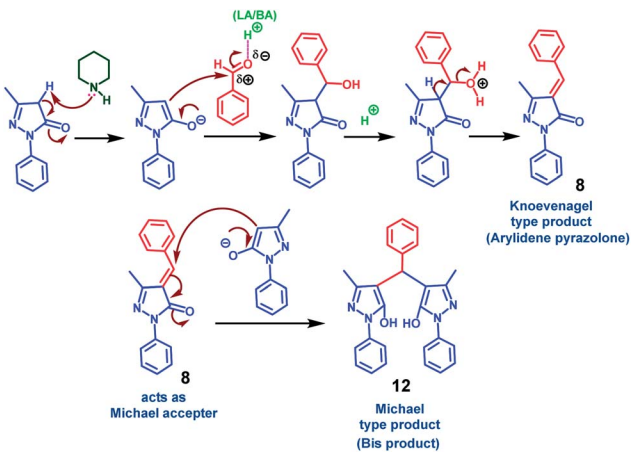


Fig. 2 A quick comparison of used surfactants on the basis of HLB values.



Scheme 3 Effect of SDS on the reaction medium.

Amphiphilic properties of the surfactant largely depend upon HLB values[11] for its hydrophilic and lipophilic character. A high HLB value of the surfactant indicates a strongly hydrophilic character, whereas a low value is an indication of a strongly hydrophobic nature. According to the HLB scale, the classification of used surfactants presented in Table 2 is shown in Fig. 2. The large HLB value of SDS shows that it is readily soluble in water compared to other surfactants and as an ionic



Scheme 4 Acid catalysed formation of the bis product.

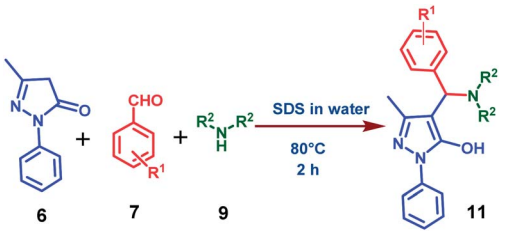
surfactant its CMC is not much affected by the increase in temperature employed in organic synthesis.[12]

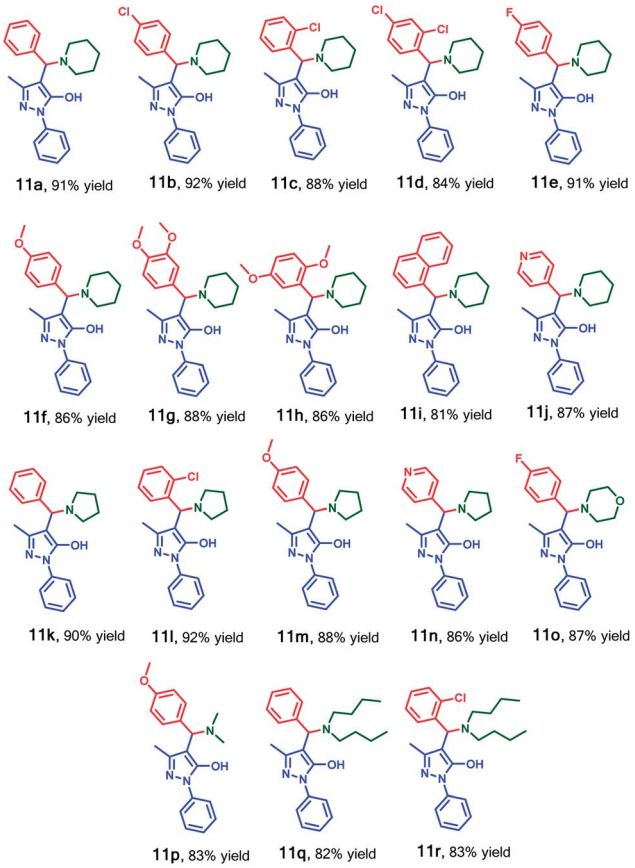
Previously, the mechanism for the direct esterification of carboxylic acids with alcohols has been reported by Kobayashi *et al.*[13a] using a surfactant-type Brønsted acid catalyst in water. Inspired from this fact, we proposed a plausible mechanism, as shown in Scheme 3.

SDS is an amphiphilic surfactant, which forms micelles in water in which hydrophilic ends arrange themselves outward and lipophilic ends arranges themselves to the inward side of the micelles. In the lipophilic pocket of a micelle, the corresponding aldehyde and secondary amine easily enter forming an imine. The water molecule, generated due to imine formation, is easily expelled from the lipophilic interior pocket to the outward side of the micelle.[13b] Therefore, the equilibrium position[14] shifts towards the imine side. SO_3O^- of SDS activates 3-methyl-1-phenyl-5-pyrazolinone by the formation of a hydrogen bond with the pyrazolic OH, favouring the nucleophilic addition towards imine followed by aromatization[15] (no need for further steps), giving the required substituted amino alkylated-1*H*-pyrazol-5-ol (Mannich type of product). Supported by the computational study, the molecular volume of the imine intermediate is approximately 170 Å^3 (calculated by Discovery studio 2.0) and according to Berkowitz *et al.*,[16] the reported hydrodynamic radius of the micelle (SDS) is about 22.0 Å (volume 44 620 Å^3). Therefore, this reveals that the imine intermediate is small enough to occupy the space inside the lipophilic core of SDS micelles.

In the absence of SDS, a secondary amine acting as a base, abstracts a proton from 3-methyl-1-phenyl-5-pyrazolinone, the position next to carbonyl finally attacks the activated carbonyl of the aromatic aldehyde to form the arylidenepyrazolone intermediate[10a,b] (Knoevenagel type). Again arylidenepyrazolone, which acts as a Michael acceptor, reacts with another molecule of 3-methyl-1-phenyl-5-pyrazolinone in the presence of a base, which finally leads to the formation of the 4,4′-(aryl methylene) bis (1-*H*-pyrazol-5-ol)[7,10c–e] (Michael type) (Scheme 4).

Table 3 SDS catalysed the synthesis of **11**[a,b]





[a] Reaction conditions: the reaction was conducted with aromatic aldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolinone (1 mmol), secondary amine (1.2 mmol) and SDS (20 mol%) in water (2 ml) at a temperature of 80 °C for 2 h. [b] All products were characterised by ^{1}H-NMR, ^{13}C-NMR, IR and Mass spectroscopy.

Conclusions

In conclusion, we have developed an economic, efficient and green, amphiphile catalysed multicomponent reaction of aromatic aldehydes, 3-methyl-1-phenyl-5-pyrazolinone and secondary amines in aqueous media. SDS (sodium dodecyl sulphate) was found to be a very useful amphiphile to catalyse the reaction *via* an imine intermediate through which the reaction proceeded in a more efficient and favourable manner *via* Mannich aromatization preferable to a Knoevenagel–Michael type reaction. The advantage of this method is to improve conditions for the synthesis of substituted 4-amino alkylated-1*H*-pyrazol-5-ol derivatives without the formation of a bis product or any side product (Table 3).

Acknowledgements

S.M., M.K.G. & R.D.S. are thankful to CSIR-UGC for financial support. We thank the SAIF division, CDRI, for providing the spectroscopic and analytical data, as well as acknowledge the financial support from CSIR-Network BSC0108. CDRI Communication no. 8832.

Notes and references

1 (*a*) C. M. Park and D. J. Jeon, *Org. Biomol. Chem.*, 2012, **10**, 2613; (*b*) W. G. Bensen, *Pain*, 2003, 515; (*c*) A. V. Ivachtchenko, *et al.*, *J. Med. Chem.*, 2011, **54**, 8161; (*d*) S. Okuno, A. Saito, T. Hayashi and P. H. Chan, *J. Neurosci.*, 2004, **24**, 7879.

2 (*a*) T. D. Penning, *et al.*, *J. Med. Chem.*, 1997, **40**, 1347–1365; (*b*) M. L. Isidro and F. Cordido, *Mini-Rev. Med. Chem.*, 2009, **9**, 664; (*c*) M. J. Genin, *et al.*, *J. Med. Chem.*, 2000, **43**, 1034; (*d*) R. Riedel, *Arzneim. Forsch.*, 1981, **31**, 655; (*e*) A. Guzman-Perez, *et al.*, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 803.

3 (*a*) S. O. Ojwach and J. Darkwa, *Inorg. Chim. Acta*, 2010, **363**, 1947; (*b*) S. Nieto, J. Pérez, L. Riera, V. Riera and D. Miguel, *Chem.–Eur. J.*, 2006, **12**, 2244; (*c*) A. Domling, *Chem. Rev.*, 2006, **106**, 17; (*d*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602.

4 (*a*) S. Kobayashi, H. Kiyohara and M. Yamaguchi, *J. Am. Chem. Soc.*, 2011, **133**, 708; (*b*) M. Hatano, T. Horibe and K. Ishihara, *J. Am. Chem. Soc.*, 2010, **132**, 56; (*c*) R. H. Qiu, S. F. Yin, X. W. Zhang, J. Xia, X. H. Xu and S. L. Luo, *Chem. Commun.*, 2009, 4759; (*d*) B. Huang, X. Yao and C.-J. Li, *Adv. Synth. Catal.*, 2006, **348**, 1528.

5 (*a*) B. H. Lipshutz, G. T. Aguinaldo, S. Ghorai and K. Voigtritter, *Org. Lett.*, 2008, **10**, 1325; (*b*) B. H. Lipshutz, D. W. Chung and B. Rich, *Org. Lett.*, 2008, **10**, 3793; (*c*) B. H. Lipshutz, S. Ghorai and G. T. Aguinaldo, *Adv. Synth. Catal.*, 2008, **350**, 953; (*d*) B. H. Lipshutz and B. R. Taft, *Org. Lett.*, 2008, **10**, 1329; (*e*) B. H. Lipshutz and A. R. Abela, *Org. Lett.*, 2008, **10**, 5329.

6 (*a*) F. M. Menger and C. E. Portnoy, *J. Am. Chem. Soc.*, 1967, **89**, 4698; (*b*) K. Fuji, T. Morimoto, K. Tsutsumi and K. Kakiuchi, *Angew. Chem.*, 2003, **115**, 2511; *Angew. Chem., Int. Ed.*, 2003, **42**, 2409.

7 (*a*) E.-S. A. Aly, M. A. Abdo and A. A. El-Gharably, *J. Chin. Chem. Soc.*, 2004, **51**, 983; (*b*) M. N. Elinson, *et al.*, *Synthesis*, 2008, **12**, 1933; (*c*) S. Sobhani, A. R. Hasaninejad, M. F. Maleki and Z. P. Parizi, *Synth. Commun.*, 2012, **42**, 2245; (*d*) E. Mosaddegh, A. Hassankhani and A. Baghizadehb, *J. Chil. Chem. Soc.*, 2010, **55**(4), 419.

8 A. Mustafa, *et al.*, *J. Am. Chem. Soc.*, 1959, **81**, 6007.

9 (*a*) A. Kumar, D. Saxena and M. K. Gupta, *Green Chem.*, 2013, **15**, 2699; (*b*) A. Kumar, M. Kumar and M. K. Gupta, *Green Chem.*, 2012, **14**, 2677; (*c*) A. Kumar, V. D. Tripathi and P. Kumar, *Green Chem.*, 2011, **13**, 51; (*d*) A. Kumar, M. Kumar, S. Maurya and R. S. Khanna, *J. Org. Chem.*, 2014, **79**, 6905; (*e*) A. Kumar, G. Gupta and S. Srivastava, *Org. Lett.*, 2011, **13**, 6366.

10 (*a*) R. Ramajayam, K.-P. Tan, H.-G. Liu and P.-H. Liang, *Bioorg. Med. Chem.*, 2010, **18**, 7849; (*b*) K. H. Mehta, *et al.*, *Chem.: Indian J.*, 2003, **1**, 38; (*c*) D. Singh and D. Singh, *J. Chem. Eng. Data*, 1984, **29**, 355; (*d*) X. L. Li, Y. M. Wang, B. Tian, M. Teruo and J. B. Meng, *J. Heterocycl. Chem.*, 1998, **35**, 129; (*e*) H. J. Ledon, *Org. Synth.*, 1988, **6**, 414.

11 (*a*) P. Krugliakov, *Physicochemical Aspects and Applications*, Elsevier Science, Amsterdam, 2000; (*b*) F. Wang, A. Klaikherd and S. Thayumanavan, *J. Am. Chem. Soc.*, 2011, **34**, 13496; (*c*) F. Tu and D. Lee, *J. Am. Chem. Soc.*, 2014, **28**, 9999.

12 (*a*) D. A. Jaeger, J. R. Wyatt and R. E. Robertson, *J. Org. Chem.*, 1985, **50**, 1467; (*b*) R. P. Bonar-Law, *J. Org. Chem.*, 1996, **61**, 3623.

13 (*a*) K. Manabe, X.-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2001, **123**, 10101; (*b*) A. Kumar, M. K. Gupta, M. Kumar and D. Saxena, *RSC Adv.*, 2013, **3**, 1673.

14 T. Hatta, *"Le Châtelier principle," The New Palgrave: A Dictionary of Economics*, 1987, vol. 3, p. 155.

15 (*a*) P. Liu, Y.-M. Pan, Y.-L. Xu and H.-S. Wang, *Org. Biomol. Chem.*, 2012, **10**, 4696; (*b*) X. Xu, M. O. Ratnikov, P. Y. Zavalij and M. P. Doyle, *Org. Lett.*, 2011, **13**, 6122.

16 (*a*) C. D. Bruce, M. L. Berkowitz, L. Perera and M. D. E. Forbes, *J. Phys. Chem. B*, 2002, **106**, 3788.