Tetrahedron 67 (2011) 4852–4857

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Microwave-assisted thermal decomposition of formamide: a tool for coupling a pyrimidine ring with an aromatic partner

Yvonnick Loidreau, Thierry Besson *

Université de Rouen, CNRS UMR 6014—C.O.B.R.A. & FR3038, I.R.C.O.F. rue Tesnière, F-76130 Mont Saint-Aignan, France

ARTICLE INFO

Article history:
Received 8 April 2011
Received in revised form 28 April 2011
Accepted 3 May 2011
Available online 17 May 2011

Keywords:
Microwave chemistry
Decomposition of formamide
Quinazolines
Dielectric properties
Niementowski reaction

ABSTRACT

Rapid and efficient generation of CO and NH_3 in the reaction mixture via microwave-assisted thermal decomposition of formamide may represent a significant improvement over existing methods for coupling a pyrimidine ring with an aromatic partner. This work aims at alerting readers on the probability to observe interesting phenomena and reactions when this very powerful heating mode is associated with thermally unstable reagents.

1. Introduction

Despite the area of microwave-assisted chemistry being twenty five years old,[1] the technique has only recently received widespread global acceptance in the academic and industrial communities. This is a consequence of the recent availability of commercial microwave systems specific for synthesis, which offer improved opportunities for reproducibility, rapid synthesis, rapid reaction optimization and the potential discovery of new chemistries.[2] The beneficial effects of microwave dielectric heating for performing organic reactions are well known (e.g., remarkable reduction of reaction time, improved yields and cleaner reactions than the one performed under conventional thermal heating).[3] They are finding an increased role in process chemistry, especially in cases when usual methods require forcing conditions or prolonged reaction times. In a large part of the examples published, it was observed that the strong heating due to specific molecules/microwaves interactions can be efficiently used for the synthesis of various heterocyclic rings for which traditional methods failed or are less attractive. In these cases, the use of adapted reactants offers operational, economic and environmental benefits over conventional methods and it allows to performed chemistry in a 'green approach'.

Among our recent projects, we decided to study the microwave stability of various solvents and reactants in order to detect the possible transformations of these molecules under microwaves and then, to study the possibility to perform novel chemical reactions. This strategy allowed us to recently explore efficient methodologies for the preparation of various quinazolin-4(3*H*)-ones as building blocks for the synthesis of derivatives of numerous bioactive molecules.[4]

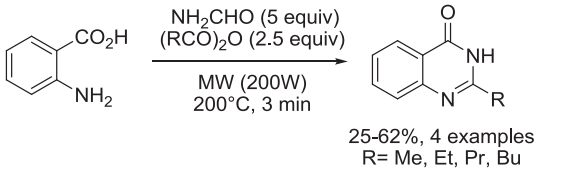
Formamide is a quite reactive polar molecule, which is commonly used either as a nucleophilic or an electrophilic agent in the synthesis of various heterocyclic rings, it possesses a high loss tangent value ($\tan \delta$=0.56)[5] that guarantees a very efficient coupling with microwaves. Taking into account all this data we re-investigated under microwaves the Niementowski synthesis of quinazolin-4(3*H*)-ones.[6] This very popular 'ancestral' reaction involves the thermal fusion of anthranilic acids with formamide. In this work we described a significant rate enhancement and demonstrated that the interesting dielectric properties of formamide and its capacity to generate heat under microwaves are useful for performing microwave-assisted chemistry. Nonetheless, in a recent study, we also revealed that microwave-promoted rapid decomposition of formamide under specific reaction conditions can be a source of ammonia that generates unexpected products.[7]

Pursuing our investigations, we were able to control the thermal decomposition of formamide under microwaves with a strict monitoring of internal temperatures using fibre-optic contact thermometers. A three-components fast (2 min) and safe synthesis of some quinazolin-4-ones was described constituting the first

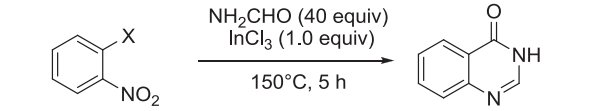
* Corresponding author. Tel.: +33 (0) 235592904, +33 (0) 235148399; fax: +33 (0) 235148423; e-mail address: thierry.besson@univ-rouen.fr (T. Besson).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.05.010

example where this reactant was used as a sole ammonia synthon for the introduction of a nitrogen atom in a heterocyclic ring under microwave irradiation (Scheme 1a).[8]



(a) Cyclocondensation of formamide with 2-aminobenzoic acid



(b) Reduction of nitro group + cyclocondensation of formamide

Scheme 1. Synthesis of quinazolinones from anthranilic acid (a) or 2-nitrobenzoic acid (b).

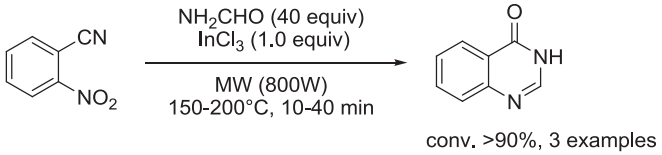
The thermal decomposition of formamide has already been described in the literature and mainly for preparing aromatic amide derivatives.[9] To our knowledge the first microwave-accelerated decomposition of formamide has been described in 2003 by a Swedish group in Uppsala University,[10] where formamide was used as combined ammonia (NH_3) synthon and carbon monoxide (CO) source in palladium-catalyzed aminocarbonylations of aryl halides. Since this date, and in connection with microwave-assisted methodologies, it has been recently exploited as both a surrogate for carbon monoxide in the synthesis of pyrazolo[1,5-*a*] and [3,4-*d*] pyrimidines[11] and for ammonia in the synthesis of pyrimido[1,2-*a*] pyrimidines.[12]

In 2008, Negrete and his group described the one-pot reductive N-heterocyclization of various 2-nitrobenzoic acid derivatives with formamide, in the presence of a molar equivalent amount of indium(III) (chloride or acetate) or bismuth(III) acetate salts.[13] They observed that formamide decomposition was promoted by the metal salts; the CO then produced allowed conversion of the aryl nitro group to arylamine and the resultant anthranilic acid derivative proceeded to Niementowski cyclocondensation to form quinazolines (Scheme 1b). In the same study they claimed that reduction of aryl nitro groups can be obtain by a long (5–10 h) heating of nitrobenzene derivatives to $InCl_3$ or $In(OAc)_3$ in refluxing *N*-methylformamide.

Considering our previous works on the synthesis of quinazolin-4(3*H*)-ones bearing a nitro group,[14] we decided to investigate the possibility to generate NH_3 and CO species in situ via microwave-accelerated heating of formamide in order to perform a one-pot procedure in which formation of the pyrimidine ring and simultaneous reduction of the starting nitro group can lead directly to amino-substituted quinazolines from the corresponding nitro-anthranilic acids and their derivatives. This paper describes a part of our investigations in the use of formamide under microwaves and it aims at alerting readers on the probability to observe interesting phenomena and reactions when this very powerful heating mode is associated with thermally unstable reagents.

2. Results and discussion

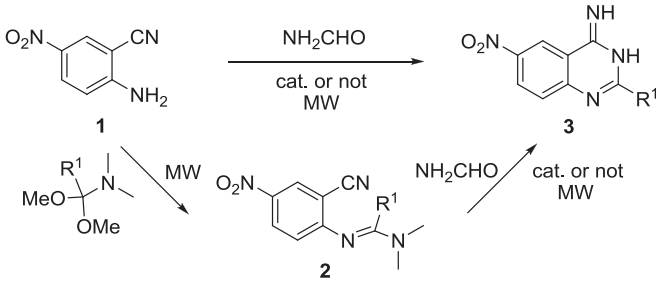
Our first approach consisted to study the method described by Negrete and his group. In connection with our recent works on the microwave-assisted decomposition of formamide we decided to transfer this thermal process into a microwave reactor in which a strict control of temperature parameters is available via an internal fibre-optic probe associated with infrared pyrometer. Then, the starting 2-nitrobenzonitrile was treated with 1 equiv of indium chloride in formamide (40 equiv) and heated for 10–40 min at various temperatures (150–200 °C). Results obtained showed a conversion of the starting material into the expected quinazolin-4-one in similar ratio to those described by Negrete (around 90%, GC analysis). Best yields were obtained when the reactions were performed at 170 °C for 40 min or at 200 °C for 10 min (Scheme 2).



Scheme 2. Intramolecular reductive N-heterocyclization of 2-nitrobenzonitrile.

To confirm the absolute necessity to have a metal salt into the mixture, the reaction was performed without $InCl_3$. The lack of attempted product confirmed that the metal salt is important into the reduction process and not only in the formamide decomposition as suggested in the reference paper. Pursuing our investigations we decided to treat *ortho*-aminobenzonitrile in the conditions described above. Our recent application of the Dimroth rearrangement incites us to start also from the 5-nitroanthranilonitrile (**1**) and its *N*-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylimidoformamides derivatives (**2a** and **2b**) themselves prepared in good yields (96 and 60%, respectively, after purification) by treatment of the starting molecule (**1**) with *N*,*N*-dimethylformamide dimethylacetal or *N*,*N*-dimethylacetamide dimethylacetal, at 70 °C in only 2 min of irradiation (800 W) at atmospheric pressure. Results given (Table 1) show that in all cases, in the presence or not of $InCl_3$, we never observed the reduction of the nitro group present on the benzenic moiety of the final product. The fact that the carbon in position 2 of the quinazoline ring was present in the starting compound (e.g., for imines **2a** and **2b**) led us to expect that the 'CO' part of formamide can be, in these cases efficiently used for the reduction of the nitro group. In fact, whatever were the conditions, all the experiments

Table 1
Synthesis of 6-nitroquinazoline-imine **3** from **1** or **2**[a]



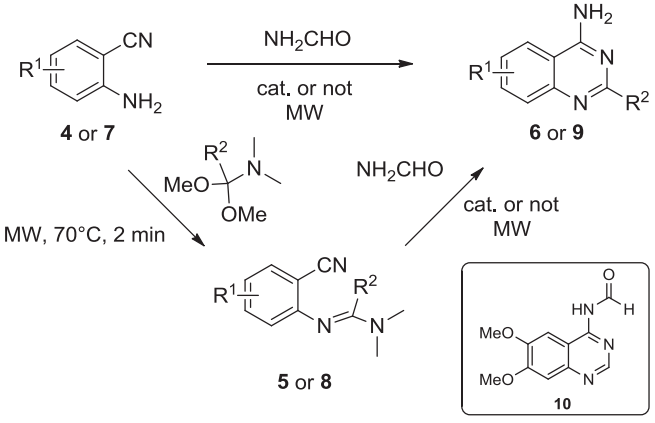
S.M.[b]	Product	R	$InCl_3$(Eq.)	T (°C)	Time (min)	Yield (%)[c]
1	**3a**	H	—	200	60	67
1	**3a**	H	1	170	30	n.d.[d]
2a	**3a**	H	—	200	10	61
2a	**3a**	H	1	150	10	68
2b	**3b**	Me	—	200	60	8[e]
2b	**3b**	Me	1	150	60	n.d.[d]

[a] Reaction were performed in sealed vials on a 1.0 mmol scale from **1** or **2** with 40 equiv of formamide and 1 equiv of $InCl_3$ (or not) under microwave at 400 W(MultiSYNTH™ from Milestone S.r.l. Italy).
[b] S.M.: starting material.
[c] Yield of isolated product.
[d] n.d.=not determined.
[e] Conversion of unisolated product.

performed from 5-nitroanthranilonitrile (**1**) or imine **2a** gave the 6-nitroquinazoline-imine (**3a**) in various yields (Table 1). The high temperatures reached into these processes have generated NH_3 into the reaction mixture via rapid decomposition of formamide. The ammonia synthon was then introduced into the final hetero-aromatic part of the quinazoline skeleton as we previously described. It should be noticed that compound **3b** was never isolated but only detected by GC/MS chromatography (Table 1).

Extending our investigations, we decided to reproduce some of these experiments starting from the unfunctionalized anthranilonitrile (**4**) or its *N*,*N*-dimethylimidoformamide derivatives (**5a** and **5b**). The starting compounds were then heated at 200 °C without $InCl_3$ or at 150–170 °C in the presence of 1 equiv of the metal salt. Here again indium trichloride helped the reaction by allowing a short decrease in the optimal temperature and sometimes reduced the time of the reaction. In all cases the final product obtained were the 4-aminoquinazoline derivatives (**6a** or **6b**) resulting from the condensation of formamide or its ammonia synthon with the starting molecule (Table 2). The yields are similar whatever conditions were used.

Table 2
Synthesis of 4-aminoquinazolines **6** or **9** from anthranilonitriles **4** or **7**[a]



S.M.[b]	Product	R^1	R^2	$InCl_3$(Eq.)	T (°C)	Time (min)	Yield (%)[c]
4	**6a**	H	H	—	200	60	69
4	**6a**	H	H	1	170	30	72
5a	**6a**	H	H	—	200	10	77
5a	**6a**	H	H	1	150	10	67
5b	**6b**	H	Me	—	200	50	89
5b	**6b**	H	Me	1	150	35	94
7	**9a**	4,5-diOMe	H	—	200	60	57
7	**9a**	4,5-diOMe	H	1	170	30	51
8a	**9a**	4,5-diOMe	H	—	200	10	50
8a	**9a**	4,5-diOMe	H	1	1500	10	55
8b	**9b**	4,5-diOMe	Me	—	170	30	65
8b	**9b**	4,5-diOMe	Me	1	150	40	68

[a] Reaction were performed in sealed vials on a 1.0 mmol scale from **4** or **7** with 40 equiv of formamide and 1 equiv of $InCl_3$ (or not) under microwave at 400 W(MultiSYNTHi™ from Milestone S.r.l. Italy).
[b] S.M.: starting material.
[c] Yield of isolated product.

In order to observe any probable effect of the substituents present on the benzenic ring, we also study the possibility to start from an electron rich anthranilonitrile derivative.

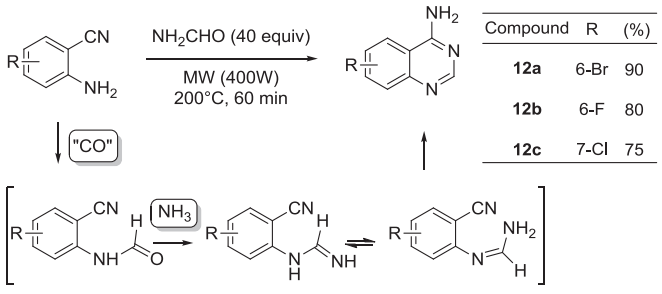
Then, 4,5-dimethoxyanthranilonitrile (**7**) and its *N*,*N*-dimethylimidoformamide analogue (**8**) were also heated in formamide in the presence, or not, of $InCl_3$. In all the experiments performed, the yields of the 4-amino-6,7-dimethoxyquinazoline (**9**) obtained were lower than those observed from the nitro substituted or the unfunctionalized anthranilonitriles (**1** and **4**, respectively). It should be noticed that at atmospheric pressure the reaction of 4,5-dimethoxyanthranilonitrile and formamide in the presence of $InCl_3$ gave a by-product identified as the *N*-(quinazolin-4-yl)formamide (**10**), which was isolated in a yield of 20% (see Table 2).

At this part of our work it is time to make some comments. The accelerated decomposition of formamide into NH_3 and CO in the presence of $InCl_3$ described in the paper of Negrete and his co-workers is not easy to appreciate in our case and we assume that the mechanism describing reduction of the nitro group, by the CO liberated in the reaction mixture, is not as simple as described. We may confirm that the metal salt is participating to the overall process of the intramolecular reductive N-heterocyclization of 2-nitrobenzonitrile and we can also suggest that the overall conditions of these experiments are in favour of the quinazolin-4-one derivatives certainly obtained after acidic hydrolysis of the intermediate quinazoline imines.

Considering our results we are not able to confirm if the addition of $InCl_3$ is really accelerating the thermal decomposition of formamide. We compared the results obtained with or without $InCl_3$ in the starting mixture and we can only say that $InCl_3$ allows a small decrease in reaction temperature without certifying that its presence helped in situ decomposition of formamide, taking in account that we recently published that formamide can start to decompose rapidly under microwaves at this temperature without any catalyst.

The use of *N*,*N*-dimethylimidoformamide derivatives of the starting anthranilonitriles showed to be an attractive method, which allows a striking reduction in reaction time (10 min instead of 40 min) and good yields in the attempted products. The rapid thermal decomposition of formamide at 200 °C has generated NH_3 synthon, which condensed rapidly with the amidines and cyclized into the quinazoline ring. This reaction is similar to the process leading to the Dimroth rearrangement in which anilines are condensed with *N*,*N*-dimethylimidoformamide derivatives to give 4-anilinoquinazolines.

During our investigations we observed that the final compounds synthesized from the unfunctionalized anthranilonitrile or its electron rich analogue (4,5-diOMe) were quinazolin-4-amine derivatives. Nevertheless, a stable tautomeric imine form was obtained in the case of electron withdrawing substituent (e.g., NO_2 group). Quinazolin-4-amine derivatives are quite rarely described in literature[15] compared to their 4-anilino analogues ,which constitute an important part of medicinal chemistry, in particular for their applications in the synthesis of tyrosine kinases inhibitors. The quinazolin-4-amines were studied for various pathologies and their synthesis was mainly patented.[16] Traditional preparation of quinazolin-4-amines involves the reaction of ammonia with 4-chloroquinazolines obtained by chlorination of the corresponding quinazolin-4-ones. The routes described above constitute interesting alternatives to this method and afford the expected products in one or two steps. In order to extend the small library prepared, we condensed various halogenated anthranilonitriles with formamide at 200 °C for 1 h under microwaves. The resulting quinazolin-4-amines (**11a**–**c**) were obtained in good yields (75–90%) (Scheme 3).



Scheme 3. Microwave-assisted Niementowski synthesis of quinazolin-4-amines (**11a**–**c**) from halogenated anthranilonitriles.

Compared with our preceding studies of the Niementowski reaction from anthranilic acid derivatives,[8] we may notice here that starting from the cyano analogues need more energy to cyclize. At this temperature and in that time, we may assume that formamide decomposed and gave NH_3 and CO synthons. In this case, it may be suggested that, after reaction of the aromatic amino group and CO, the intermediate formamide derivative was attacked by the residual NH_3 and cyclized to afford the final quinazoline ring (Scheme 3).

3. Conclusion

In conclusion, we confirm that rapid and efficient generation of ammonia in the reaction mixture via microwave-assisted thermal decomposition of formamide may represent a significant improvement over existing methods for coupling a pyrimidine ring with an aromatic partner. The procedure, which consists to start from the *N*,*N*-dimethylimidoformamide derivatives is then really a safe and comfortable process (150 °C), which may avoid miscellaneous drawbacks. Our work is alerting readers on the probability to observe various and interesting phenomena when this very powerful heating mode is associated with thermally unstable reagents (e.g., formamides, dimethylsulfoxide), which can be the source of various key reactants (carbon monoxide, amines, formyl group and formate) in organic synthesis. Users of these classes of compounds should be attentive to the fact that usual, but sometimes slow, thermal unexpected processes can be dramatically accelerated under microwaves. Considering the recent work of Cataldo and his co-workers on the synthesis of HCN polymers from thermal decomposition of formamide,[17] we also assume that the conditions described in our studies (150 °C, 170 °C or 200 °C) are limiting the possible appearance of hydrogen cyanide, which is known to be produced when thermal decomposition of formamide is performed at 200–220 °C during several hours. Further investigations extending the families of heterocyclic precursors are underway.

4. Experimental section

4.1. General

All reactions were monitored by thin-layer chromatography with silica gel 60 F_{254} pre-coated aluminium plates (0.25 mm). Melting points of solid compounds were measured on a WME Köfler hot-stage with a precision of ±2 °C and are uncorrected. IR spectra were recorded on a Perkin–Elmer IRFT 1650 spectrometer. Liquids were applied as a film between KBr windows and solids were dispersed in a KBr pellet. Absorption bands are given in cm^{-1}.

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Brucker DXP 300 spectrometer at 300, 75 and 282 MHz, respectively. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet and m: multiplet. Coupling constants *J* are in hertz and chemical shifts are given in parts per million and calibrated with DMSO-d_6 or D_2O (residual solvent signals). Mass spectra analysis was performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters LCP 1er XR spectrometer.

Microwave experiments were conducted in sealed vials or at atmospheric pressure in two commercial microwave reactors especially designed for synthetic chemistry. The 'hybrid' microwave platform MultiSYNTH™ (Milestone S.r.l. Italy) is a dedicated microwave system for synthetic applications. The instrument features a special shaking system that ensures high homogeneity of the reaction mixtures. It is equipped with an indirect pressure-control through pre-calibrated springs at the bottom of the vessels shields and with both, contact-less infrared pyrometer (IRT) and fibre-optic contact thermometer (FO) for accurate temperature measurement. It is noteworthy that the IRT can be calibrated directly on the temperature read by the FO to ensure the highest accuracy and reproducibility. START SYNTH (Milestone S.r.l. Italy) is a multimode cavity with a microwave power delivery system ranging from 0 to 1200 W. Open vessel experiments were carried out in a 250 mL round bottom flask fitted with a reflux condenser. The temperature was monitored via a fibre-optic contact thermometer protected in a Teflon-coated ceramic well inserted directly in the reaction mixture. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature and power profiles were monitored in both cases through the EASYControl software provided by the manufacturer.

4.2. General procedures for the syntheses of formimidamide and acetimidamide derivatives

Benzonitriles were suspended in 2.5 equiv of *N*,*N*-dimethylformamide dimethylacetal or *N*,*N*-dimethylacetamide dimethylacetal and were irradiated at 1200 W under microwaves. The resulting mixture was cooled to room temperature and refrigerated overnight. The precipitate formed was filtered, washed with diethyl ether and dried. Purification by column chromatography over silica gel using CH_2Cl_2/PE (5:5, v/v) as the eluent gave the desired compound.

*4.2.1. (E)-N′-(2-Cyano-4-nitrophenyl)-N,N-dimethylformimidamide (**2a**) (lit.[14]).* Starting from 2-amino-5-nitrobenzonitrile **1** (50.0 g; 0.36 mol) and *N*,*N*-dimethylformamide dimethylacetal (102 mL; 0.77 mol), **2a** was obtained after an irradiation at 70 °C during 2 min as a yellow solid (64.2 g; 96%); mp 149 °C; IR (KBr) $\nu_{max}(cm^{-1})$: 2971, 2901, 2224, 1623, 1593, 1558, 1499, 1414, 1374, 1310, 1280, 1170, 1141, 1076, 922, 888, 829, 776, 754, 726, 658; ^1H NMR (300 MHz, DMSO-d_6): δ 8.48 (d, 1H, J=3 Hz, H-3), 8.27 (m, 2H, J_1=3 Hz, J_2=9 Hz, NC*H*N and H-5), 7.38 (d, 1H, J=9 Hz, H-6), 3.16 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.5 (C-1), 156.7 (C-7), 140.0 (C-4), 129.5 (C-3), 128.6 (C-5), 118.4 (C-6), 116.8 (*C*N), 105.9 (C-2), 34.4 (N(*C*H_3)$_2$); HRMS calcd for $C_{10}H_{10}N_4O_2$ $[M+H]^+$ 219.0882 found 219.0873.

*4.2.2. (E)-N′-(2-Cyano-4-nitrophenyl)-N,N-dimethylacetimidamide (**2b**).* Starting from 2-amino-5-nitrobenzonitrile **1** (4.46 g; 27.4 mmol) and *N*,*N*-dimethylacetamide dimethylacetal (10 mL; 68.4 mmol), **2b** was obtained after an irradiation at 90 °C during 2 min as a yellow solid (3.56 g; 57%); mp 131 °C; IR (neat) $\nu_{max}(cm^{-1})$: 2938, 2227, 1584, 1549, 1504, 1395, 1329, 1298, 1169, 1132, 1076, 901, 842, 777, 768, 736, 656; ^1H NMR (300 MHz, DMSO-d_6): δ 8.52 (d, 1H, J=3 Hz, H-3), 8.26 (dd, 1H, J_1=3 Hz, J_2=9 Hz, H-5), 6.92 (d, 1H, J=9 Hz, H-6), 3.10 (br s, 6H, N(*C*H_3)$_2$), 2.05 (s, 3H, *C*H_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4 (C-1), 159.8 (C-7), 139.7 (C-4), 129.3 (C-3), 128.5 (C-5), 122.8 (C-6), 116.8 (*C*N), 105.3 (C-2), 40.3 (N(*C*H_3)$_2$), 15.9 (C-8); HRMS calcd for $C_{11}H_{13}N_4O_2$ $[M+H]^+$ 233.1039 found 233.1033.

*4.2.3. (E)-N′-(2-Cyanophenyl)-N,N-dimethylformimidamide (**5a**) (lit.[14]).* Starting from anthranilonitrile **4** (5.0 g; 42.3 mmol) and *N*,*N*-dimethylformamide dimethylacetal (14 mL; 105.6 mmol), **5a** was obtained after an irradiation at 90 °C during 15 min as a pale yellow solid (5.7 g; 79%); mp 66 °C; IR (KBr) $\nu_{max}(cm^{-1})$: 2912, 2215, 1979, 1628, 1588, 1557, 1474, 1447, 1415, 1366, 1280, 1254, 1222, 1172, 1118, 1098, 969, 942, 870, 846, 758, 736; ^1H NMR (300 MHz, DMSO-d_6): δ 7.93 (s, 1H, NC*H*N), 7.58 (dd, 1H, J_1=1 Hz, J_2=7 Hz, H-3), 7.47 (td, 1H, J_1=1 Hz, J_2=9 Hz, H-5), 7.14 (d, 1H, J=7 Hz, H-6), 7.00 (t, 1H, J=9 Hz, H-4), 3.07 (s, 3H, NCH_3), 2.99 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.0 (C-7), 154.9 (C-1), 133.7 (C-5), 132.9

(C-3), 121.6 (C-4), 119.0 (C-6), 118.6 (*C*N), 105.8 (C-2), 34.0 (N(*C*H$_3$)$_2$); HRMS calcd for $C_{10}H_{11}N_3$ $[M+H]^+$ 174.1031 found 174.1040.

*4.2.4. (E)-N′-(2-Cyanophenyl)-N,N-dimethylacetimidamide (**5b**) (lit.[14]).* Starting from anthranilonitrile **4** (2.0 g; 16.9 mmol) and *N*,*N*-dimethylacetamide dimethylacetal (6.2 mL; 42.3 mmol), **5b** was obtained after an irradiation at 115 °C during 2 min as white needles (2.41 g; 78%); mp 68 °C; IR (neat) ν_{max}(cm^{-1}): 2931, 2214, 1575, 1550, 1442, 1413, 1395, 1363, 1314, 1290, 1218, 1191, 1168, 1022, 959, 875, 839, 182, 755, 722; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61 (dd, 1H, J_1=1 Hz, J_2=7 Hz, H-3), 7.49 (td, 1H, J_1=1 Hz, J_2=8 Hz, H-5), 7.01 (td, 1H, J_1=1 Hz, J_2=7 Hz, H-4), 6.78 (dd, 1H, J_1=1 Hz, J_2=8 Hz, H-6), 3.02 (br s, 6H, N(C*H*$_3$)$_2$), 1.89 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.9 (C-7), 155.4 (C-1), 133.5 (C-5), 132.7 (C-3), 123.0 (C-4), 121.0 (C-6), 118.4 (*C*N), 105.0 (C-2), 37.6 (N(*C*H$_3$)$_2$), 14.9 (C-8); HRMS calcd for $C_{11}H_{14}N_3$ $[M+H]^+$ 187.1179 found 187.1178.

*4.2.5. (E)-N′-(2-Cyano-4,5-dimethoxyphenyl)-N,N-dimethylformimidamide (**8a**).* Starting from 4,5-dimethoxybenzonitrile **7** (4.0 g; 22.5 mmol) and *N*,*N*-dimethylformamide dimethylacetal (7.5 mL; 56.12 mmol), **8a** was obtained after an irradiation at 90 °C during 10 min as a pale yellow solid (3.98 g; 77%); mp 120 °C; IR (neat) ν_{max}(cm^{-1}): 3011, 2916, 2813, 2215, 1623, 1602, 1560, 1495, 1419, 1378, 1248, 1213, 1198, 1121, 1099, 1033, 998, 888, 855, 830; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.92 (s, 1H, NC*H*N), 7.09 (s, 1H, H-3), 6.74 (s, 1H, H-6), 3.82 (s, 3H, OC*H*$_3$), 3.72 (s, 3H, OC*H*$_3$) 3.05 (s, 3H, NC*H*$_3$), 2.96 (s, 3H, NC*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.5 (C-5), 153.3 (C-7), 150.6 (C-4), 143.9 (C-1), 119.1 (*C*N), 114.1 (C-3), 102.6 (C-6), 95.8 (C-2), 55.9 (O*C*H$_3$), 55.6 (O*C*H$_3$), 33.9 (N(*C*H$_3$)$_2$); HRMS calcd for $C_{12}H_{16}N_3O_2$ $[M+H]^+$ 234.1243 found 234.1243.

*4.2.6. (E)-N′-(2-Cyano-4,5-dimethoxyphenyl)-N,N-dimethylacetimidamide (**8b**).* Starting from 4,5-dimethoxybenzonitrile **7** (1.0 g; 5.6 mmol) and *N*,*N*-dimethylacetamide dimethylacetal (2.1 mL; 14.0 mmol), **8b** was obtained after an irradiation at 80 °C during 6 min. The crude product was previously purified directly by column chromatography and gave **8b** (1.31 g; 95%) as an orange oil; IR (neat) ν_{max}(cm^{-1}): 2935, 2210, 1593, 1494, 1440, 1416, 1381, 1365, 1251, 1214, 1189, 1174, 1113, 1020, 1003, 948, 843, 765, 754; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.10 (s, 1H, H-3), 6.36 (s, 1H, H-6), 3.77 (s, 3H, OC*H*$_3$), 3.73 (s, 3H, OC*H*$_3$) 3.00 (br s, 6H, N(C*H*$_3$)$_2$), 1.87 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1 (C-7), 153.1 (C-5), 151.4 (C-4), 143.4 (C-1), 118.8 (*C*N), 113.8 (C-3), 106.5 (C-6), 94.6 (C-2), 55.9 (O*C*H$_3$), 55.6 (O*C*H$_3$), 37.5 (N(*C*H$_3$)$_2$), 15.0 (C-8); HRMS calcd for $C_{13}H_{18}N_3O_2$ $[M+H]^+$ 248.1399 found 248.1393.

4.3. General procedures for the syntheses of quinazolin4-amines

All quinazolines could be obtained by two methods. Each derivative was described once using the best method.

Method A: Benzonitriles were suspended in formamide (40 equiv) and $InCl_3$ (1 equiv), or not, in a sealed vial and were irradiated at 400 W under microwaves. The residue was cooled to room temperature, filtrated, washed with water and dried.

Method B: Formimidamide or acetimidamide intermediates were suspended in formamide (40 equiv) and $InCl_3$ (1 equiv), or not, in a sealed vial and were irradiated at 400 W under microwaves. The residue was cooled to room temperature, filtrated, washed with water and dried.

In the two methods, purification by column chromatography over silica gel using a gradient of CH_2Cl_2/EtOAc (from 100/0 to 0/100, v/v) as the eluent gave the desired compounds.

*4.3.1. 6-Nitroquinazolin-4-(3H)-imine (**3a**).* Starting from 2-amino-5-nitrobenzonitrile **1** (0.2 g; 0.92 mmol) and formamide (1.46 mL; 36.66 mmol), **3a** was obtained following Method A after an irradiation at 200 °C during 60 min as a dark solid (117 mg; 67%); mp 336 °C; IR (neat) ν_{max}(cm^{-1}): 3084, 1952, 1681, 1618, 1587, 1510, 1482, 1341, 1320, 1284, 1260, 1199, 1094, 927, 904, 847, 806, 749, 742, 636; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.33 (d, 1H, J=2 Hz, H-7), 8.58 (br s, 1H, N*H*), 8.53 (s, 1H, H-2), 8.48 (dd, 1H, J_1=2 Hz, J_2=9 Hz, H-5), 8.25 (br s, 1H, N*H*), 7.81 (d, 1H, J=9 Hz, H-8); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.8 (C-4), 158.6 (C-8a), 153.2 (C-6), 143.8 (C-2), 129.0 (C-7), 126.5 (C-8), 121.4 (C-5), 113.3 (C-4a); HRMS calcd for $C_8H_7N_4O_2$ $[M+H]^+$ 191.0569 found 191.0564.

*4.3.2. 2-Methyl-6-nitroquinazolin-4-(3H)-imine (**3b**).* Starting from acetimidamide derivative **2b** (0.29 g; 1.25 mmol) and formamide (2.0 mL; 50.17 mmol), **3b** was converted (8%) following Method B after an irradiation at 200 °C during 60 min but could not be isolated.

*4.3.3. Quinazolin-4-amine (**6a**).* Starting from formimidamide derivative **5a** (0.22 g; 1.25 mmol) and formamide (2.0 mL; 50.17 mmol), **6a** was obtained following Method B after an irradiation at 200 °C during 10 min as a yellow solid (140 mg; 77%); mp 274 °C; IR (neat) ν_{max}(cm^{-1}): 3076, 2718, 1948, 1684, 1614, 1580, 1559, 1514, 1483, 1457, 1364, 1321, 1290, 1203, 1117, 1023, 921, 757, 736, 629; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (s, 1H, H-2), 8.20 (d, 1H, J=8 Hz, H-8), 7.77 (m, 3H, J_1=1 Hz, J_2=8 Hz, H-5 and N*H*$_2$), 7.66 (d, 1H, J=8 Hz, H-7), 7.48 (td, 1H, J_1=1 Hz, J_2=8 Hz, H-6); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7 (C-4), 155.4 (C-2), 149.6 (C-8a), 132.7 (C-7), 127.3 (C-8), 125.3 (C-5), 123.5 (C-6), 114.3 (C-4a); HRMS calcd for $C_8H_8N_3$ $[M+H]^+$ 146.0718 found 146.0714.

*4.3.4. 2-Methylquinazolin-4-amine (**6b**) (lit.[15b]).* Starting from acetimidamide derivative **5b** (0.235 g; 1.25 mmol), formamide (2.0 mL; 50.17 mmol) and $InCl_3$ (0.277 g; 1.25 mmol), **6b** was obtained following Method B after an irradiation at 150 °C during 35 min as a pale yellow solid (0.187 g; 94%); mp 306 °C; IR (neat) ν_{max}(cm^{-1}): 2886, 1560, 1508, 1466, 1396, 1369, 1324, 1128, 1056, 986, 875, 744, 640; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, 1H, J=8 Hz, H-8), 7.72 (m, 3H, J_1=1 Hz, J_2=8 Hz, H-5 and N*H*$_2$), 7.67 (d, 1H, J=8 Hz, H-7), 7.39 (td, 1H, J_1=1 Hz, J_2=8 Hz, H-6); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.6 (C-4), 162.9 (C-2), 150.1 (C-8a), 132.6 (C-7), 126.7 (C-8), 124.4 (C-5), 123.4 (C-6), 112.5 (C-4a), 25.8 (*C*H$_3$); HRMS calcd for $C_9H_{10}N_3$ $[M+H]^+$ 160.0875 found 160.0863.

*4.3.5. 6,7-Dimethoxyquinazolin-4-amine (**9a**).* Starting from 4,5-dimethoxybenzonitrile **7** (0.227 g; 1.25 mmol) and formamide (2.0 mL; 50.17 mmol), **9a** was obtained following Method A after an irradiation at 200 °C during 60 min as a pale yellow solid (0.146 g; 57%); mp 202 °C; IR (neat) ν_{max}(cm^{-1}): 3335, 3082, 1676, 1585, 1476, 1452, 1438, 1337, 1283, 1248, 1220, 1196, 1165, 1115, 1029, 990, 847, 835, 785, 721, 667, 630; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25 (s, 1H, H-2), 7.56 (s, 1H, H-8), 7.40 (br s, 2H, N*H*$_2$), 7.05 (s, 1H, H-5), 3.89 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4 (C-4), 153.9 (C-7), 153.8 (C-2), 148.1 (C-6), 146.8 (C-8a), 107.9 (C-4a), 106.7 (C-8), 102.6 (C-5), 55.9 (O*C*H3), 55.6 (O*C*H3); HRMS calcd for $C_{10}H_{12}N_3O_2$ $[M+H]^+$ 206.0930 found 206.0928.

*4.3.6. 2-Methyl-6,7-dimethoxyquinazolin-4-amine (**9b**).* Starting from acetimidamide **8b** (0.31 g; 1.25 mmol), formamide (2.0 mL; 50.17 mmol) and $InCl_3$ (0.277 mg; 1.25 mmol), **9b** was obtained following Method B after an irradiation at 150 °C during 40 min as a yellow solid (0.186 g; 68%); mp >350 °C; IR (neat) ν_{max}(cm^{-1}): 3117, 2163, 1683, 1574, 1500, 1438, 1386, 1289, 1215, 1099, 774; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52 (s, 1H, H-8), 7.30 (br s, 2H, N*H*$_2$), 7.00 (s, 1H, H-5), 3.86 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 2.36 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7 (C-4), 160.5 (C-7), 153.9 (C-2), 147.5 (C-6), 147.1 (C-8a), 106.5 (C-4a), 105.9 (C-8), 102.6 (C-5),

56.0 (OCH3), 55.5 (OCH3), 25.6 (CH3); HRMS calcd for $C_{11}H_{14}N_3O_2$ $[M+H]^+$ 220.1086 found 220.1077.

*4.3.7. N-(6,7-Dimethoxyquinazolin-4-yl)formamide (**10**).* Starting from 4,5-dimethoxybenzonitrile **7** (0.227 g; 1.25 mmol) and formamide (2.0 mL; 50.17 mmol), **10** was a by-product obtained following Method A, after an irradiation at 170 °C during 10 min as a brown solid (0.058 g; 20%); mp 265 °C; IR (neat) $\nu_{max}(cm^{-1})$: 3240, 2917, 1921, 1698, 1480, 1423, 1377, 1358, 1257, 1227, 1214, 1198, 1191, 1139, 1047, 987, 850, 838, 772, 741, 693, 628; ^1H NMR (300 MHz, DMSO-d_6): δ 11.37 (d, 1H, J=9 Hz, NHCO), 9.68 (d, 1H, J=9 Hz, NCOH), 8.66 (s, 1H, H-2), 7.82 (s, 1H, H-8), 7.28 (s, 1H, H-5), 3.96 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.3 (C-4), 155.4 (NCO), 154.2 (C-7), 152.1 (C-2), 149.7 (C-6), 148.2 (C-8a), 108.7 (C-4a), 106.8 (C-8), 101.4 (C-5), 56.2 (OCH3), 56.0 (OCH3); HRMS calcd for $C_{11}H_{12}N_3O_3$ $[M+H]^+$ 234.0879 found 234.0871.

*4.3.8. 6-Bromoquinazolin-4-amine (**12a**).* Starting from 2-amino-5-bromobenzonitrile **11a** (0.15 g; 0.76 mmol) and formamide (1.20 mL; 30.50 mmol), **12a** was obtained following Method A after an irradiation at 200 °C during 60 min as a pale orange solid (0.152 g; 90%); mp >350 °C; IR (neat) $\nu_{max}(cm^{-1})$: 3306, 3109, 2173, 1916, 1668, 157, 1549, 1497, 1472, 1355, 1318, 1287, 1265, 1123, 1026, 918, 866, 844, 828, 622; ^1H NMR (300 MHz, DMSO-d_6): δ 8.51 (d, 1H, J=2 Hz, H-5), 8.41 (s, 1H, H-2), 7.88 (br dd, 3H, J_1=2 Hz, J_2=9 Hz, H-7 and NH_2), 7.61 (d, 1H, J=9 Hz, H-8); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.7 (C-4), 155.6 (C-2), 148.0 (C-8a), 136.2 (C-7), 129.3 (C-8), 125.9 (C-5), 117.9 (C-6), 115.3 (C-4a); HRMS calcd for $C_8H_7BrN_3$ $[M+H]^+$ 223.9823 found 223.9828.

*4.3.9. 6-Fluoroquinazolin-4-amine (**12b**).* Starting from 2-amino-5-fluorobenzonitrile **11b** (0.171 g; 1.25 mmol) and formamide (2.0 mL; 50.17 mmol), **12b** was obtained following Method A after an irradiation at 200 °C during 60 min as a pale yellow solid (0.165 g; 80%); mp 329 °C; IR (neat) $\nu_{max}(cm^{-1})$: 3277, 3090, 2238, 1942, 1675, 1583, 1565, 1513, 1488, 1437, 1368, 1327, 1276, 1256, 1213, 1038, 906, 872, 861, 831, 760, 713; ^1H NMR (300 MHz, DMSO-d_6): δ 8.38 (s, 1H, H-2), 8.05 (dd, 1H, J_1=3 Hz, J_2=10 Hz, H-7), 7.80 (br s, 2H, NH_2), 7.72 (m, 2H, J_1=3 Hz, J_2=10 Hz, H-8 and H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.5–161.4 (C-6), 157.2 (C-4), 154.9 (C-2), 146.7 (C-8a), 130.2–130.1 (C-8), 122.3–122.0 (C-7), 114.7–114.6 (C-4a), 107.8–107.5 (C-5); HRMS calcd for $C_8H_7FN_3$ $[M+H]^+$ 164.0624 found 164.0615.

*4.3.10. 7-Chloroquinazolin-4-amine (**12c**).* Starting from 2-amino-4-chlorobenzonitrile **11c** (0.192 g; 1.25 mmol) and formamide (2.0 mL; 50.17 mmol), **12c** was obtained following Method A after an irradiation at 200 °C during 60 min as a yellow solid (0.170 g; 75%); mp 322 °C; IR (neat) $\nu_{max}(cm^{-1})$: 3078, 1950, 1682, 1574, 1559, 1468, 1447, 1376, 1352, 1321, 1281, 1257, 1164, 1074, 924, 883, 867, 828, 777, 740, 640, 630; ^1H NMR (300 MHz, DMSO-d_6): δ 8.40 (s, 1H, H-2), 8.25 (d, 1H, J=9 Hz, H-8), 7.94 (br s, 2H, NH_2), 7.70 (d, 1H, J=2 Hz, H-5), 7.54 (dd, 1H, J_1=2 Hz, J_2=9 Hz, H-6); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.6 (C-4), 156.6 (C-2), 150.6 (C-9), 137.3 (C-7), 126.1 (C-8), 125.8 (C-6), 125.8 (C-5), 112.9 (C-10); HRMS calcd for $C_8H_7ClN_3$ $[M+H]^+$ 180.0329 found 180.0310.

Acknowledgements

This work was supported by a grant from the Région Haute-Normandie (YL) and the ISCE-CHEM program. We acknowledge Milestone S.r.l. (Italy) for the provision of the microwave reactors and financial and technical support.

References and notes

1. Giguere, R. L.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *41*, 4945–4948 This paper is considered as the first paper reporting the interest of microwave heating in organic synthesis.
2. For the most cited book see:*Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006.
3. For recent reviews see: (a) Kappe, C. O.; Dallinger, D. *Mol. Diversity* **2009**, *13*, 71–193; (b) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325–3355; (c) For a recent paper on the thermal effect of microwaves see: Obermayer, D.; Guttmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321–8324.
4. Besson, T.; Chosson, E. *Comb. Chem. High Troughput Screening* **2007**, *10*, 903–917.
5. For more details see: Gabriel, C.; Gabriel, S.; Grant, E. J.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223 Lost dissipation factor (tan δ) expresses the capacity of a molecule or a material to transform electromagnetic energy into thermal energy. A high susceptibility to microwaves is characterized by a high value of tan δ.
6. Alexandre, F.-R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911–3913.
7. Kostakis, I. K.; Elomri, H.; Seguin, E.; Iannelli, M.; Besson, T. *Tetrahedron Lett.* **2007**, *48*, 6609–6613.
8. Nouira, I.; Kostakis, I. K.; Dubouilh, C.; Chosson, E.; Iannelli, M.; Besson, T. *Tetrahedron Lett.* **2008**, *49*, 7033–7036.
9. (a) Back, R. A.; Boden, J. C. *Trans. Faraday Soc.* **1971**, *67*, 88–96; (b) Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306–2309; (c) Bahadur, S.; Srivastana, N.; Mukherji, S. *Curr. Sci.* **1983**, *52*, 910–912; (d) Kakumoto, T.; Saito, K.; Imamura, A. *J. Phys. Chem.* **1985**, *89*, 2286–2291.
10. Wan, Y.; Alterman, M.; Larhed, M.; Halberg, A. *J. Comb. Chem.* **2003**, *5*, 82–84; Three years later the same group published an alternative microwave-assisted aminocarbonylation protocol using hydroxylamine hydrochloride as a convenient solid ammonia equivalent: Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* **2006**, *62*, 4665–4670.
11. Daniels, N. R.; Kim, K.; Lebois, E. P.; Muchalski, A.; Hughes, M.; Linsley, C. W. *Tetrahedron Lett.* **2008**, *49*, 305–310.
12. Grosjean, S.; Triki, S.; Meslin, J. C.; Julienne, D.; Deniaud, D. *Tetrahedron* **2010**, *66*, 9912–9924.
13. Kundu, S. K.; Mahindaratne, P. D.; Quintero, M. V.; Bao, A.; Negrete, G. R. *ARKIVOC* **2008**, *i*, 33–42.
14. Foucourt, A.; Dubouilh-Benard, C.; Chosson, E.; Corbière, C.; Buquet, C.; Iannelli, M.; Leblond, B.; Marsais, F.; Besson, T. *Tetrahedron* **2010**, *66*, 4495–4502.
15. For the most recent (a) and cited (b) papers see : (a) Yang, X.; Liu, H.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Synlett* **2010**, 101–106; (b) Seijas, J. A.; Vasquez-Tato, M. P.; Martinez, M. M. *Tetrahedron Lett.* **2000**, *41*, 2215–2217.
16. For a list of patents see Refs. 7–10 in Ref. 15a and Refs. 7–12 in Ref. 15b.
17. Cataldo, F.; Patane, G.; Compagnoni, G. *J. Macromol. Sci., Part A: Pure Appl. Chem.* **2009**, *46*, 1039–1048.