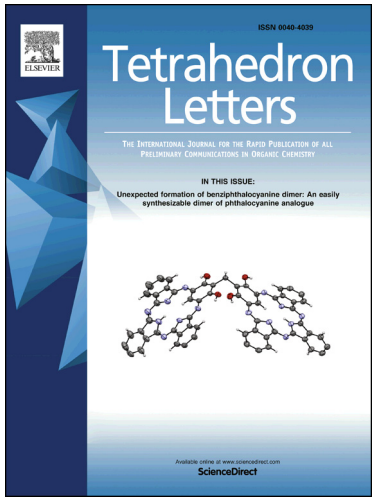


Regio-specific synthesis of new 1-(*tert*-butyl)-1H-pyrazolecarboxamide derivatives

Santiago Matías Ruatta, Marcelo César Murguía, Carmen Ramírez de Arellano, Santos Fustero

PII: S0040-4039(17)30607-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.05.029
Reference: TETL 48922

To appear in: *Tetrahedron Letters*

Received Date: 10 March 2017
Revised Date: 2 May 2017
Accepted Date: 10 May 2017

Please cite this article as: Ruatta, S.M., Murguía, M.C., Ramírez de Arellano, C., Fustero, S., Regio-specific synthesis of new 1-(*tert*-butyl)-1H-pyrazolecarboxamide derivatives, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.05.029

Regio-specific synthesis of new 1-(*tert*-butyl)-1H-pyrazolecarboxamide derivatives

Santiago Matías Ruatta[a]; Marcelo César Murguía[a,b*]; Carmen Ramírez de Arellano[c]; Santos Fustero[d,e]

[a] Laboratorio de Química Aplicada (LAQUIMAP). Facultad de Bioquímica y Ciencias Biológicas. Universidad Nacional del Litoral (UNL). CC 242 Ciudad Universitaria, Ruta Nacional 168. C.P.: S3000ZAA. Santa Fe, Argentina.

[b] Grupo de Medio Ambiente. Instituto de Desarrollo Tecnológico para la Industria Química (INTEC). Güemes 3450. C.P.: 3000. Santa Fe, Argentina.

[c] Departamento de Química Orgánica. Universidad de Valencia and Centro de Innovación en Química Avanzada (ORFEO−CINQA), E-46100, Valencia, Spain.

[d] Departamento de Química Orgánica. Facultad de Farmacia. Universitat de València. Vicente Andrés Estelles s/n. C.P.: 46100. Burjassot, Valencia, Spain.

[e] Laboratorio de Moléculas Orgánicas. Centro de Investigación Príncipe Felipe, C.P.: 46012, Valencia, Spain.

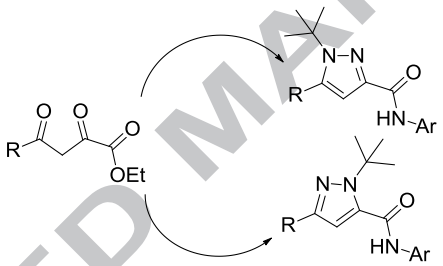
*Corresponding Author: mmurguia@santafe-conicet.gov.ar

Tel: +54 (0) 342 455 9174 / 77 - Int. 2080

Fax: +54 (0) 342 451 1079

[†]At the memory of the Prof. Dr. José Barluenga Mur

Supporting Information Placeholder



ABSTRACT: Regio-specific and non-regiospecific condensation reactions on 1,3-dicarbonyl compounds rendered 1,3,5-trisubstituted pyrazoles. Herein, the control of regio-specificity was a significant improvement in pyrazole research. A high yield acylation of poorly nucleophilic aryl amines, which resulted in mono- or diacylated products depending on the reaction conditions, is described. As a result, a library of potentially bioactive compounds was obtained.

Keywords:

Pyrazole carboxamide

Regio-specific condensation

Arylamine acylation

tert-Butyl hydrazine

Diacylation

Introduction

The pyrazole ring is present in many synthetic and pharmaceutical compounds possessing a wide range of biological activities such as antimicrobial,[1-7] antiviral,[8] anti-inflammatory,[9] antihistaminic,[10] pesticidal,[11] antifungal,[12,13] anticonvulsant,[14-16] antidepressant,[17] antipyretic[18,19] and anticancer[20,21] properties. These bioactivities have inspired chemists to synthesize substituted pyrazole systems to explore the usefulness of this heterocyclic template.

Among them, pyrazole carboxamide derivatives represent an attractive target not only from a synthetic point of view but also because of the interesting biological properties they present. Some representative bioactive pyrazole carboxamides are bixafen (Bayer Crop Science), a crop protection agent (Fig.1 a), [22] and the non-fluorinated pyrazol carboxamide SR-144528 which behaves as a MAPK inhibitor (Fig.1 c).[23] The 3-trifluoromethyl-1-methyl-pyrazole motif is also present in non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex (Fig.1 b).[24]

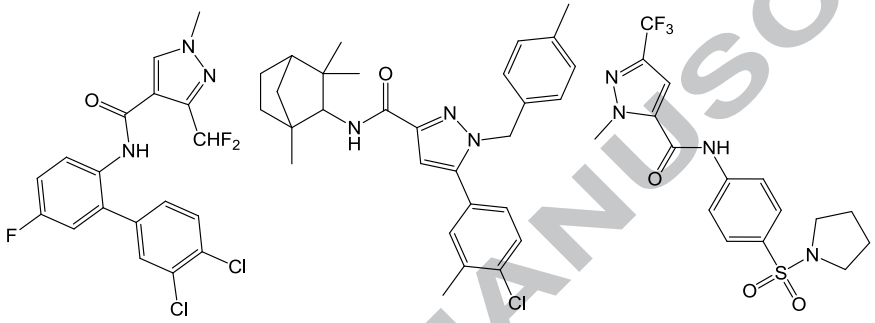


Figure 1. Examples of bioactive pyrazole carboxamides.

The condensation of hydrazines with 1,3-dicarbonyl compounds is a classic method for constructing the 1H-pyrazole ring. However, although excellent in terms of yield, the method suffers from poor regio-selectivity in many cases, depending on the nature of the substrates and reaction conditions. Therefore, an adequate methodology for the synthesis of a particular regio-isomer has been the objective of research for the last decades. Previous papers described reaction conditions that improved regio-selectivity, but failed to establish a truly regio-specific reaction.[25] Herein, an unreported regio-specific variant of this reaction to obtain 1-(*tert*-butyl)-1*H*-pyrazole-3-esters is described (Figure 2, Step I).

The obtained products were then functionalized to obtain 1-(*tert*-butyl)-1*H*-pyrazole-3-carboxamides[26] (Figure 2, Step II). The classic amine acylation technique proved inefficient against poorly nucleophylic aryl amines. Hence, we describe suitable conditions to afford high yields of carboxamides even when aryl amines have electron withdrawing groups in different positions.

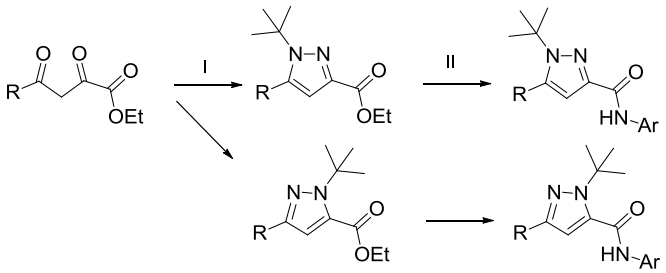
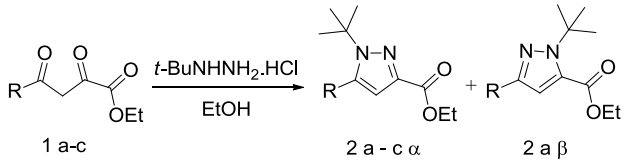


Figure 2. Main reactions in the present work.

Results and discussion

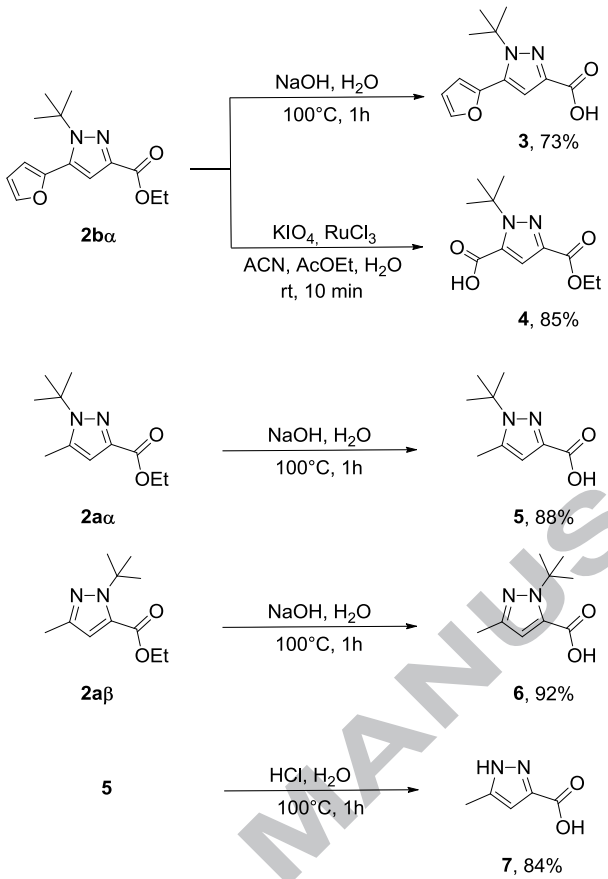


Scheme 1. Condensation of pyrazole ring from different substrates.

Entry	R	Products	Yield %
1	Methyl	**2aα, 2aβ**	34:66 (53)
2	2- Furyl	**2bα**	100
3	Phenyl	**2cα**	73

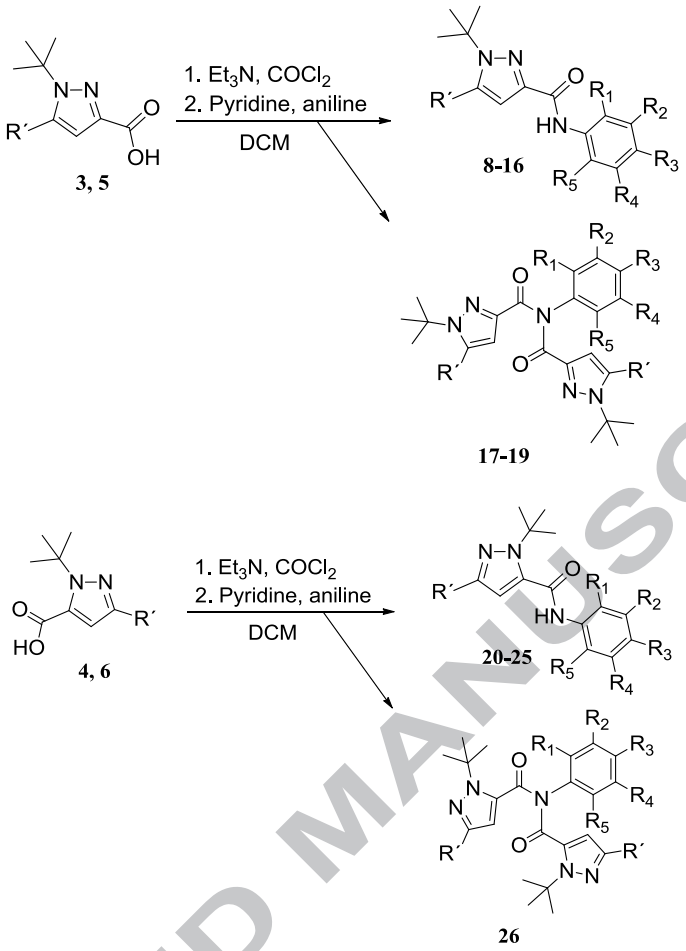
Table 1. Substrate influence on the regio-selectivity of pyrazole condensation.

The condensation of the pyrazole ring from 1,3-dicarbonyl compounds was performed in ethanol at room temperature. A regio-specific reaction was obtained when using compounds 1b and 1c as starting materials, while the use of compound 1a afforded a mixture of isomers (Table 1). Although the furyl- and phenyl-groups were likely to be responsible for this specific condensation. Previous experience has, however, shown that compound 1b resulted in a mixture of isomers when reacted with methyl hydrazine.[16] Therefore, the sterical interaction between the bulky *tert*-butyl and the furyl- and phenyl-groups might play a crucial role in the orientation of the reaction.



Scheme 2. Hydrolysis, oxidation and deprotection to obtain carboxylic acid derivatives.

In order to obtain the 1*H*-pyrazole-3-carboxylate, the ester group of **2b** was hydrolysed in a 6M NaOH solution, affording good yields. The 1*H*-pyrazole-5-carboxylate was obtained through oxidation of the furyl-group of **2b**, a previously reported reaction for similar compounds.[16] Additionally, free *N*-H-pyrazoles can be obtained by deprotection of the *tert*-butyl derivative, as exemplified for **5**. In this case, heating to reflux in 1M HCl for 1h afforded compound **7** in good yield[27] (Scheme 2).



Scheme 3. Acylation of substituted aryl amines.

Entry	Product	Ac:An	R´	R_1	R_2	R_3	R_4	R_5	Yield %
4	**8**	2:1	2-Furyl	H	H	H	H	H	95
5	**9**	2:1	2-Furyl	H	H	NO_2	H	H	79
6	**10**	2:1	2-Furyl	F	F	F	F	F	72
7	**11**	2:1	2-Furyl	F	H	Br	H	F	55
8	**12**	2:1	2-Furyl	H	F	F	F	H	95
9	**13**	2:1	2-Furyl	F	H	F	H	F	90
10	**14, 17**	2:1	2-Furyl	Cl	H	CF_3	H	Cl	18, 10
11	**14**	1:3	2-Furyl	Cl	H	CF_3	H	Cl	24
12	**17**	3:1	2-Furyl	Cl	H	CF_3	H	Cl	97
13	**15**	2:1	Methyl	H	H	H	H	H	92
14	**16**	2:1	Methyl	H	H	NO_2	H	H	74
15	**18**	2:1	Methyl	F	F	F	F	F	55
16	**19**	2:1	Methyl	Cl	H	CF_3	H	Cl	71

17	**20**	2:1	Ethoxycarbonyl	H	H	H	H	H	100
18	**21**	2:1	Ethoxycarbonyl	H	H	NO_2	H	H	80
19	**22**	2:1	Ethoxycarbonyl	F	F	F	F	F	49
20	**23**	2:1	Ethoxycarbonyl	Cl	H	CF_3	H	Cl	98
21	**24**	2:1	Methyl	H	H	H	H	H	60
22	**25**	2:1	Methyl	H	H	NO_2	H	H	81
23	**26**	2:1	Methyl	F	F	F	F	F	48

Table 2. 1*H*-pyrazole-carboxamides obtained.

The reaction of compound **3**, as acyl chloride derivative, with different aryl amines in the presence of pyridine was completed after 20 h and afforded the corresponding 1*H*-pyrazole-3-carboxamide derivatives **8-13** in good yields. Also, compounds **14** and **17** were obtained with varying yields, depending on the reaction conditions. The classic methodology,[28-30] originally used to attach aliphatic amines to the acyl chloride, was not suitable to afford high yields when aryl amines with electron withdrawing groups were used. When working with poorly nucleophilic aryl amines, an excess of acyl chloride was found to improve yields significantly. The exceeding acyl chloride ensures an absolutely anhydrous and favourable system for this reaction. The remaining unreacted compound **3** can be recovered. Also, the reaction rates improved significantly when pyridine was used both as a solvent and catalyst.

Compounds **8-13** (Scheme 3) were obtained in good yields. Surprisingly, the use of [2,6-dichloro-4-(trifluoromethyl)]-phenyl amine afforded two different products, **14** and **17**. When a 2/1 acid/aryl amine relationship was used, both products appeared, with the mono-acyl derivative **14** being predominant. In this case, 28.6 % of the aryl amine (limitant reagent) reacted to obtain mono-acyl derivative **14**, while the rest of the crude mixture did not react. Then, mono-acyl (around 37%) reacted with a second acyl chloride of **3** to give diacyl derivative **17**. The fact that the acyl chloride is more prone to react with the mono-acyl derivative than the aryl amine is evident.

We obtained mono-acyl derivative **14** as the only product by using a 1/3 acid/aryl amine relationship, yielding 24 % of the isolated product. As the yields show, the formation of **14** was unfavourable, which could be due to the inductive effect of the chlorine atoms in the *ortho*-position of the aryl amine. But, unlike the other mono-acyl derivatives obtained, the amide nitrogen of this product seems nucleophilic enough to attack a second carbonyl carbon spontaneously. A similar case was previously reported[4] and the authors proposed a plausible mechanism that explains this behaviour.

The following entries reproduce the reaction from different substrates affording analogous results except for compound **18**, the only case in which a pentafluoroaniline underwent double acylation.

Single crystals of compound 9 suitable for X-ray diffraction experiments were obtained by slow evaporation in ^{i}PrOH.[31] The crystal structure confirms the regio-chemistry with the *tert*-butyl group bonded to the nitrogen atom labelled N(11) (Figure 3).

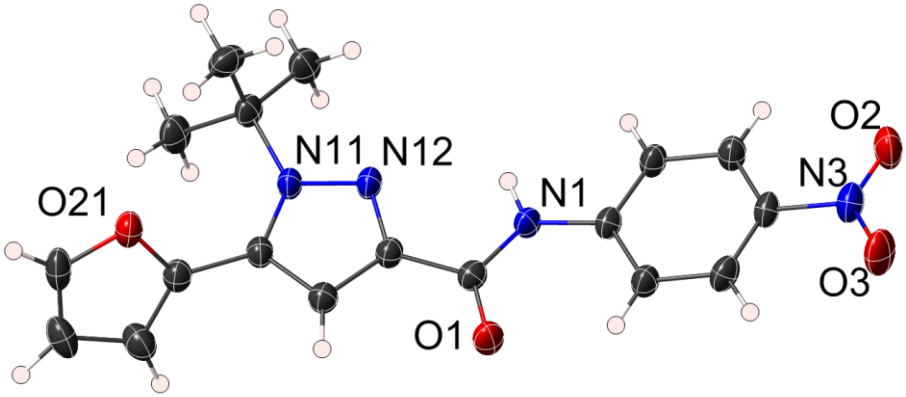


Figure 3. Ellipsoid plot of compound **9** (50% probability level) showing the labelling scheme. Carbon and hydrogen atom labels have been omitted for clarity.

Conclusions

In this study, a novel case of regio-specific pyrazole ring condensations, presumably driven by a steric effect, are reported. These findings are likely to facilitate the design of future reactions aiming at the obtention of specific pyrazole regio-isomers. This reaction is environmentally-friendly, and has no special requirements other than the bulky structure of some substituents.

Also, we developed convenient preparative procedures for the efficient synthesis of previously unknown 1-(*tert*-butyl-1*H*-pyrazole-carboxamides. The optimized technique allows acylating almost any aryl amine with acceptable yields, independent of the electrophilicity of their substituents.

The acylation of aryl amines resulted in mono- or diacylated products depending on the reaction conditions. These results agree with previous findings, reinforcing current theories for the reaction mechanism.[29, 30]

The above-described approach is well suitable for the construction of novel pyrazoles of potential pharmacological interest. The newly synthesized compounds are bound to attract interest as potentially biologically active substances as well as precursors and reagents for the design of complex poly-functional structures.

Acknowledgments

Financial support from the Universidad Nacional del Litoral (UNL) is gratefully acknowledged. We thank SCSIE-UV for the X-ray facilities.

Supporting Information Available. CCDC 1536511 contain the supplementary crystallographic data for compound **9** (www.ccdc.cam.ac.uk/data_request/cif).

References

1. Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449.
2. Ranjana, A.; Vinod, K.; Rajiv, K.; Shiv, P. S. *Beilstein J. Org. Chem.* **2011,** *7*, 179–197.
3. Elguero, J. In *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, pp 167–303.
4. Elguero, J. In *Comprehensive Heterocyclic Chemistry II;* Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 3, pp 1–75.
5. Kost, A. N.; Grandberg, I. I. In *Advances in Heterocyclic Chemistry;* Katritzky, A. R.; Boulton, A. J., Eds.; Academic Press: New York, 1966; Vol. 6, pp 347 ff.
6. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003,** *44*, 6737–6740.
7. Wiley, R. H.; Wiley, P. *Pyrazolones, Pyrazolidones and Derivatives;* John Wiley and Sons: New York, 1964.
8. Behr, L. C.; Fusco, R.; Jarboe, C. H. In The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings; Weissberger, A., Ed.; Interscience Publishers: New York, 1967.
9. David, D. P.; Martin, D. J.; Charles, M. D. F. 5-Aminopyrazoles useful as selective inhibitors of the protein tyrosine kinase P56ick. WO 9740019 (A1), Nov 30, 1997.
10. Kordik, C. P.; Luo, C.; Zanoni, B. C.; Lovenberg, T. W.; Wilson, S. J.; Vaidya, A. H.; Crooke, J. J.; Rosenthal, D. I.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 2287–2290.
11. Nakazato, A.; Okuyama, S. *Drugs Future* **1999,** *24*, 1089–1098.
12. Meegalla, S. K.; Doller, D.; Sha, D.; Soll, R.; Wisnewski, N.; Silver, G. M.; Dhanoa, D. *Bioorg. Med. Chem. Lett.* **2004,** *14*, 4949–4953.
13. Huppatz, J. L. *Aust. J. Chem.* **1985,** *38*, 221–230.
14. Fustero, S.; Sanz-Cervera, J.F.; Simón-Fuentes, A.; Román, R.; Catalán, S.; Murguía, M.C. *Biologically oriented molecules, synthesis*. ACS Symposium Series Book 1003, Academic Press: New York, 2009, pp. 182-209.
15. Sanz-Cervera, J.F.; Blasco, R.; Piera, J.; Cynamon, M.; Ibáñez, I.; Murguía, M.C.; Fustero, S. *J. Org. Chem.* **2009**, *74*, 8988-8996.
16. Fustero, S.; Roman, R., Sanz Cervera, J.; Simon, A.; Cunat, A.; Villanova, S.; Murguía, M.C. *J. Org. Chem.* **2008**, *73*, 3523-3529.
17. Baasner, B.; Hagemann, H.; Tatlow, J. C. (2000) In Houben-Weyl Organo-Fluorine Compounds Volume E 10 a-c, Thieme Stuttgart-NewYork.
18. Banks, R. E., Smart, B. E., Tartlow, J.C. Ed. In Organofluorine Chemistry: Principles and Commercial Applications, Plenun Press, New York, 1994.
19. Schlosser, M. *Angew. Chem. Int. Ed.* 1998, *37*, 1496-1513.
20. Shamroukh, A. H.; Rashad, A. E.; Sayed, H. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005,** *180*, 2347–2360.
21. Carter, T. A.; Wodicka, L. M.; Shah, N. P.; Velasco, A. M.; Fabian, M. A.; Treiber, D. K.; Milanov, Z. V.; Atteridge, C. E.; Biggs, W. H.; Edeen, P. T.; Floyd, M.; Ford, J. M.; Grotzfeld, R. M.; Herrgard, S.; Insko, D. E.; Mehta, S. A.; Patel, H. K.; Pao, W.; Sawyers, C. L.; Varmus, H.; Zarrinkar, P. P.; Lockhart, D. J. *Proc. Natl. Acad. Sci. U. S. A.* **2005,** *102*, 11011–11016.
22. Giornal, F.; Landelle, G.; Lui, N.; Vors, J. P.; Pazenok, S.; Leroux, F. R. *Org. Process Res. Dev.* **2014**, *18*, 1002−1009.
23. Persson, T.; Yde, C. W.; Rasmussen, J. E.; Rasmussen, T. L.; Guerra, B.; Issinger, O-G.; Nielsen, J. *Org. & Biomol. Chem.*, **2007**, 5, 3877 - 4024
24. . Fustero, S.; Fuentes, A. S.; Delgado, O.; Román, R. In *Fluorine in Heterocyclic Chemistry*. Springer Int. Publ. EU, 2014; Vol I, pp 279 - 322.
25. Moura, S.; Flores, A. F. C.; Favero, R. P.; Pinto, E.; Machado, P.; Martins, M. A. P. *Lett Org. Chem*. **2008**, *5*, 91-97.
26. Bobko, M. A., Kaura, A. C., Evans, K. A., Su, D-S.; *Org. Lett.* **2012**, *14*, 3906-3908.
27. Ermolenko, M. S.; Guillou, S.; Janin, Y. L.; *Tetrahedron*, **2013,** 69, 257-263.
28. Biradar, A. V.; Umbarkar, S. B.; Dongare, M. K.; *Applied Catalysis A: General* 285. **2005**, 190–195.
29. Nagaraj, R. A.; Kumar V. S.; *Can. J. Chem*. **1984**, *62***,** 1292-1296
30. Fun, H. K.; Quah, C. K., Chandrakantha, B.; Isloor, A. M.; Shetty, P.; *Acta Cryst.*, **2010**, *E66*, 66-74.
31. Sheldrick, G. M.; *Acta Cryst.*, **2015**, *C71*, 3-8.
32. Sheldrick, G. M.; *Acta Cryst.*, **2008**, *A64*, 112-122.

Highlights

•We have found a regio-specific condensation of *tert*-butyl hydrazine with certain dicarbonilic compounds.

•We have developed a high yield acylation reaction for poorly nucleophilic aryl amines.

•The present work reports a wide library of new compounds with similar structures to commercial bioactives.